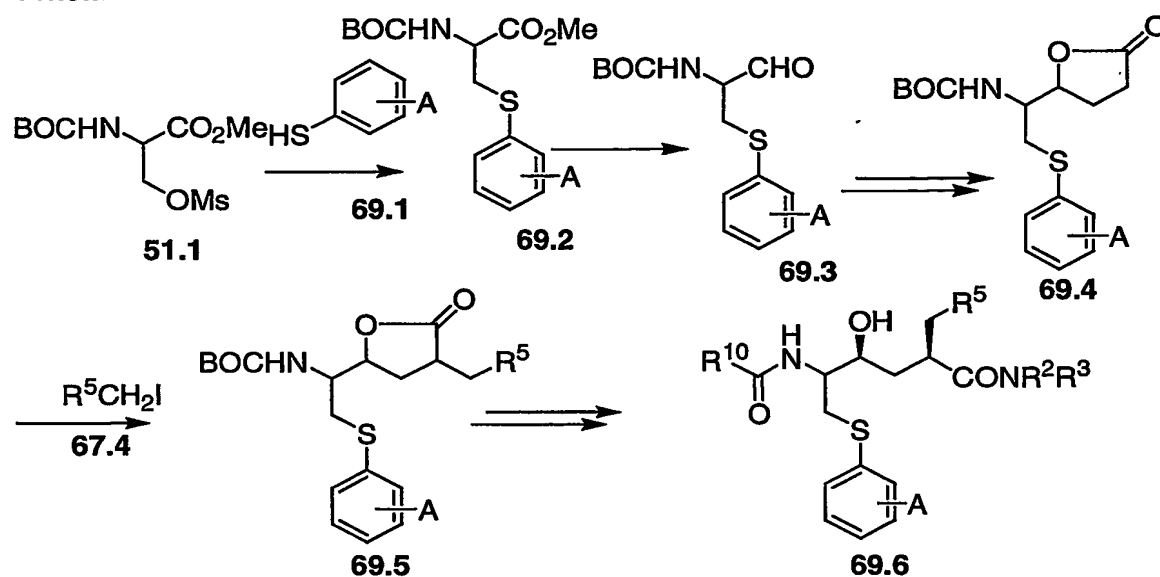
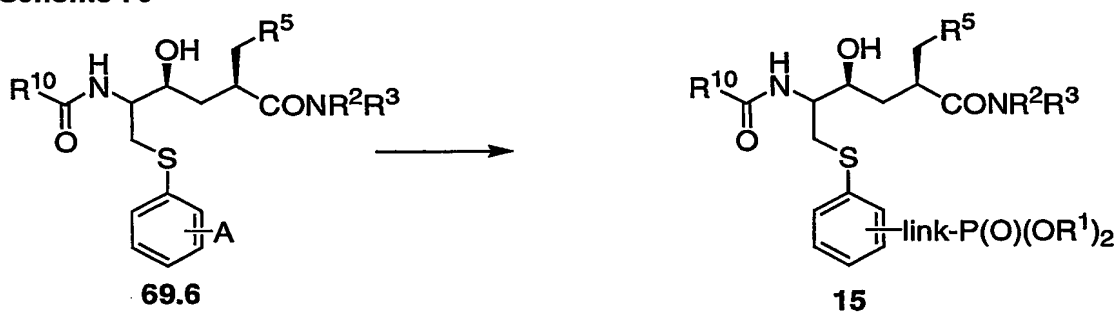


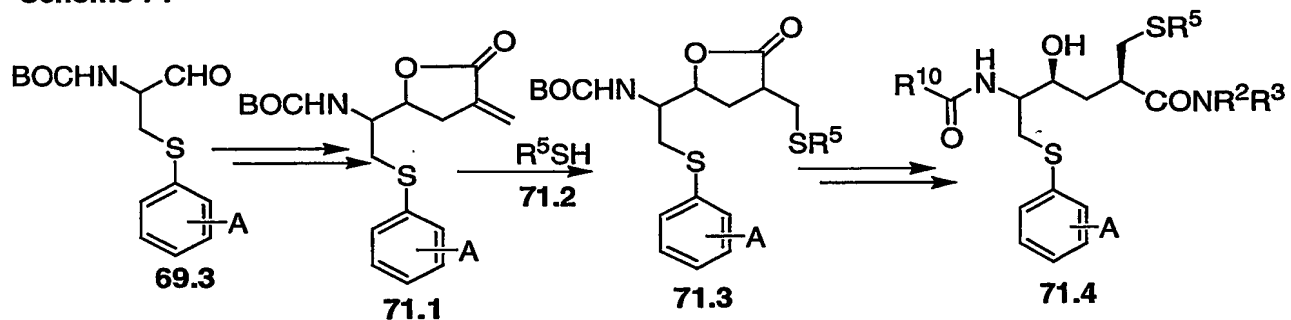
Scheme 69



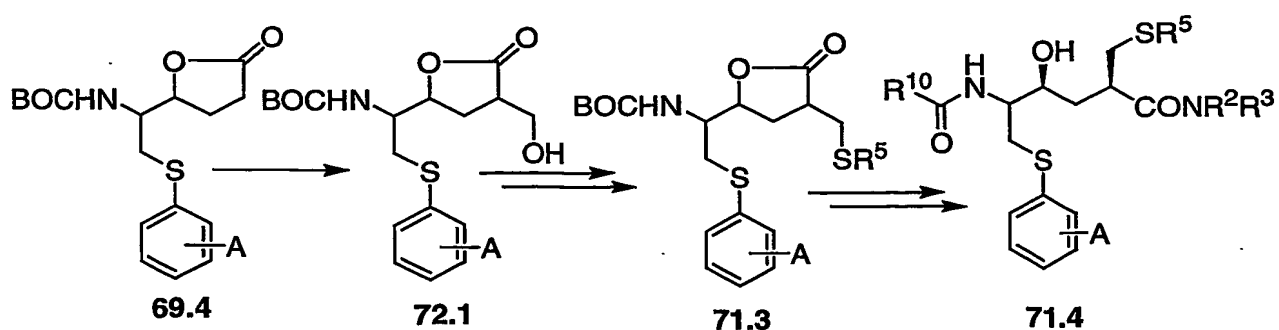
Scheme 70



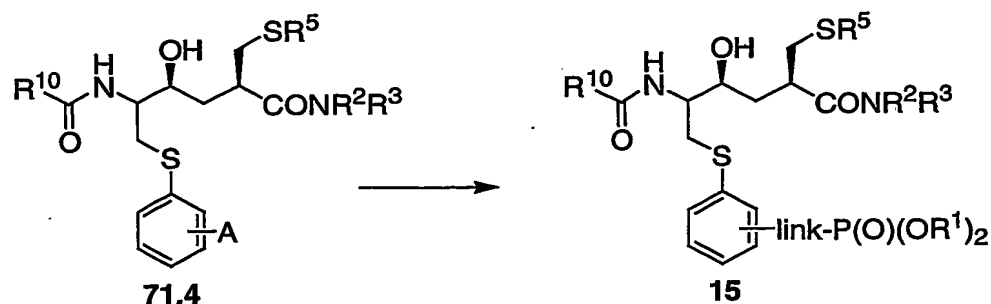
Scheme 71



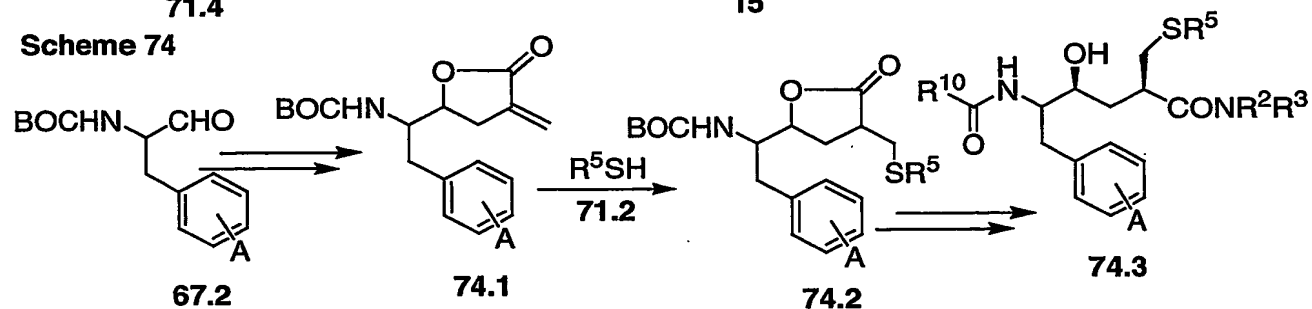
Scheme 72



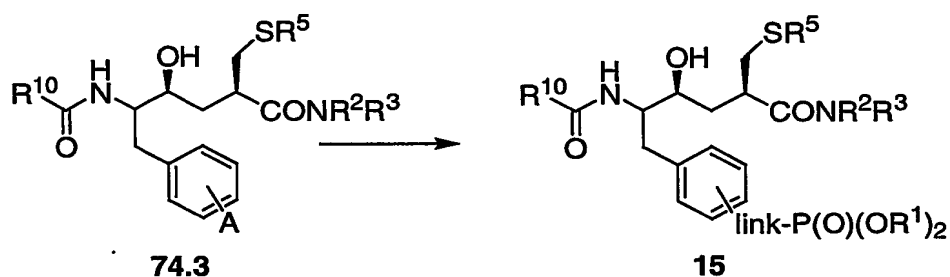
Scheme 73



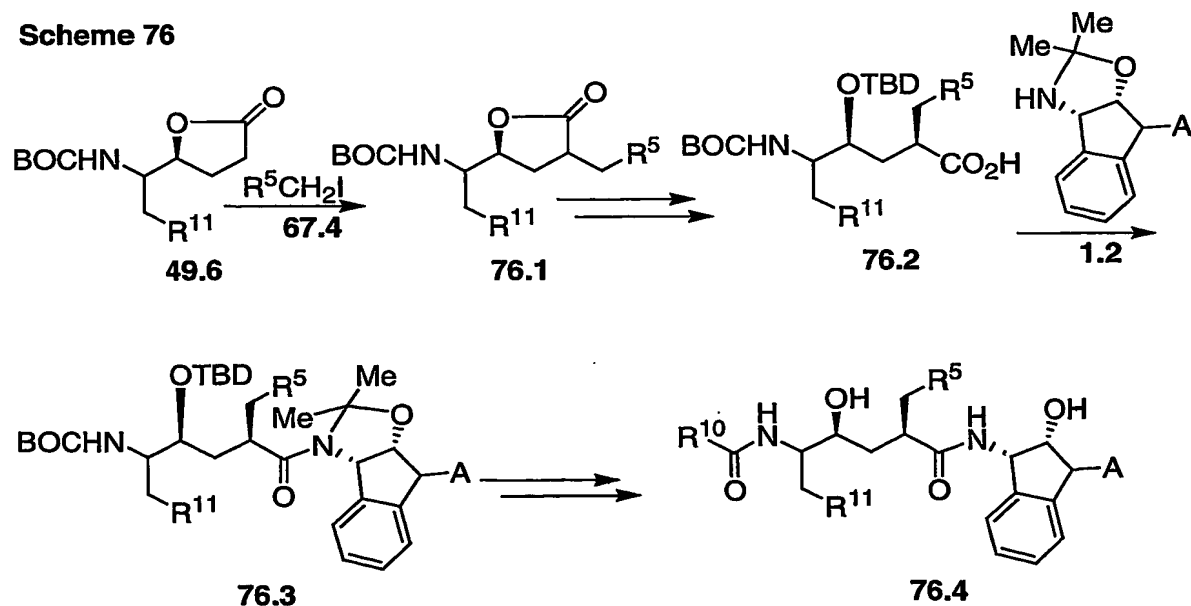
Scheme 74



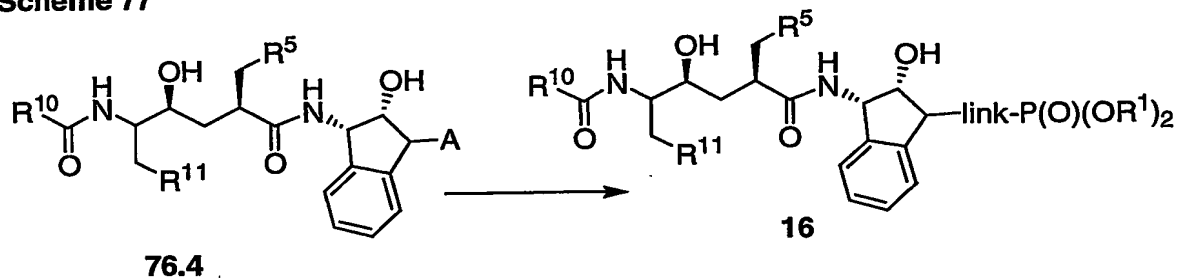
Scheme 75



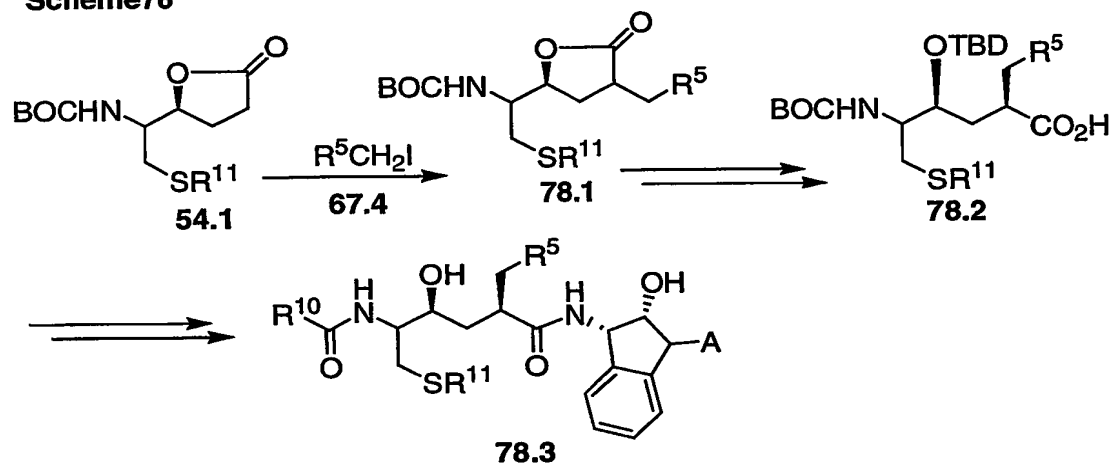
Scheme 76



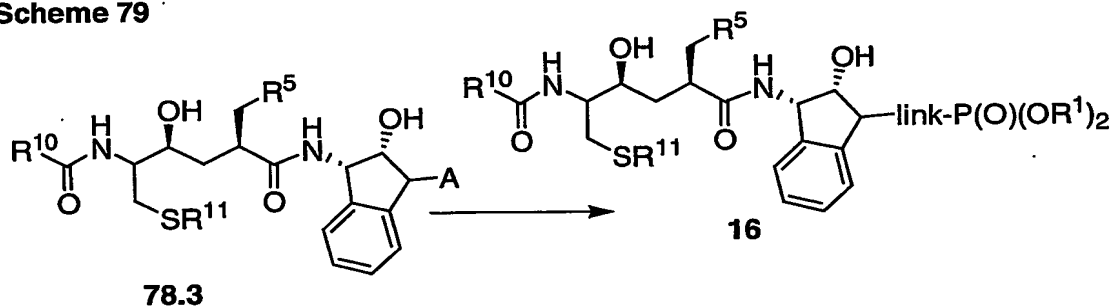
Scheme 77



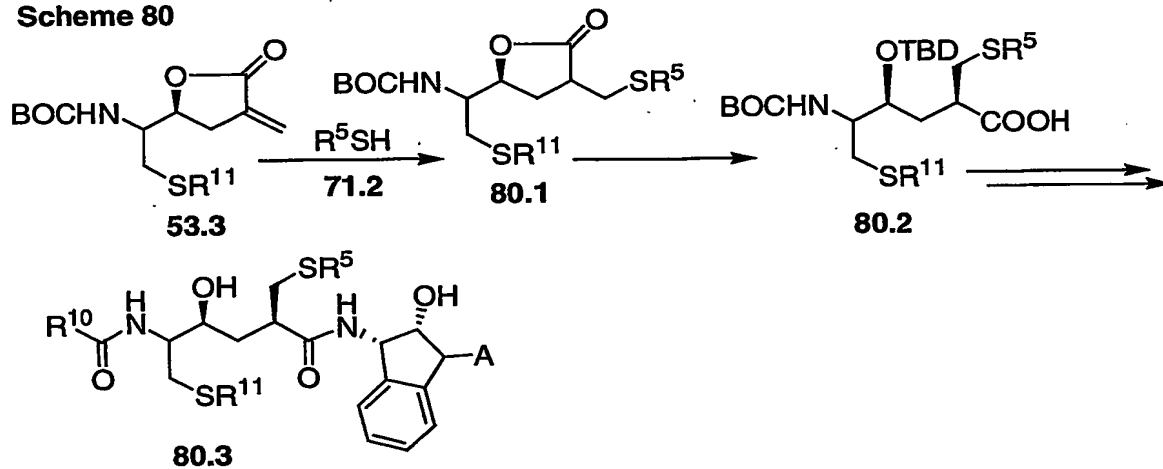
Scheme 78



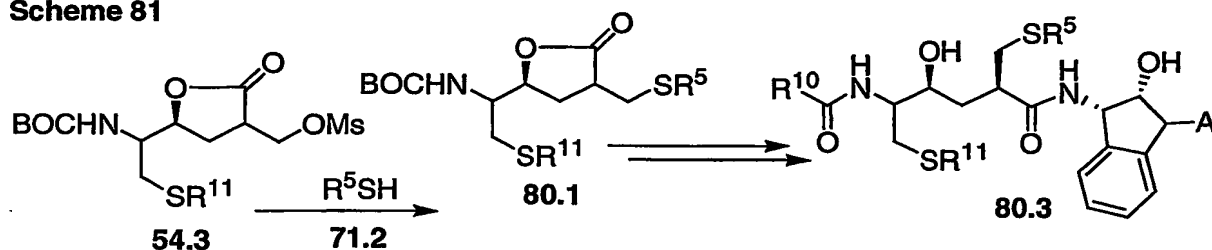
Scheme 79



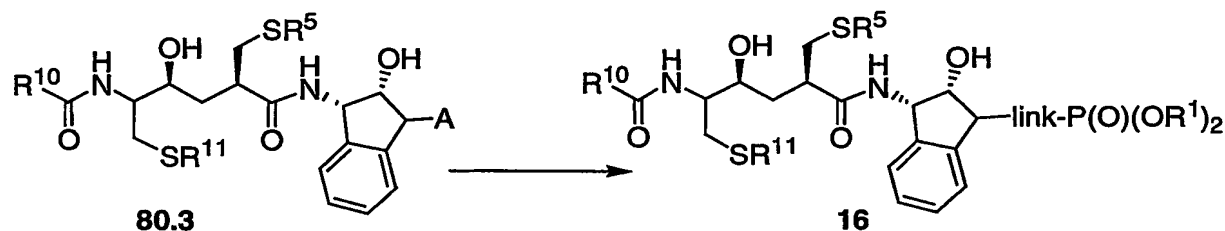
Scheme 80



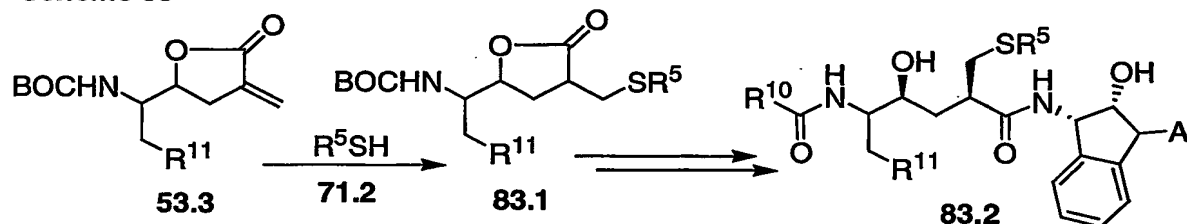
Scheme 81



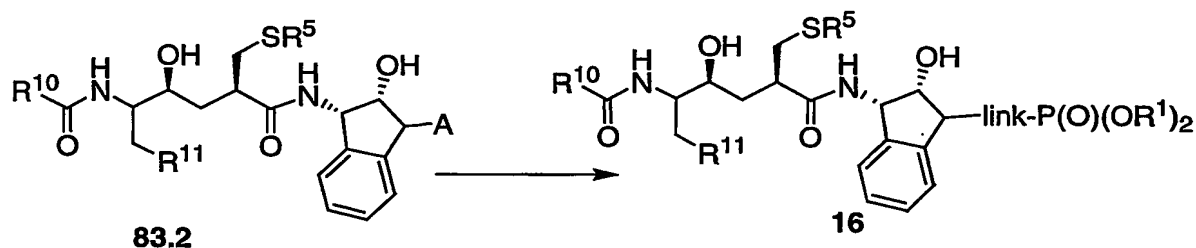
Scheme 82



Scheme 83



Scheme 84



Preparation of the phosphonate ester intermediates 17 in which X and X' are direct bonds.

Schemes 85 and 86 illustrate the preparation of the phosphonate esters 17 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the aminochroman derivative 33.1 to afford the amide 85.1. The product is then converted, as described in Scheme 49, into the diamide 85.2.

The reactions shown in Scheme 85 illustrate the preparation of the compounds 85.2 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as $[OH]$, $[SH]$, $[NH]$, Br. Scheme 86 depicts the conversion of the compounds 85.2 in which A is $[OH]$, $[SH]$,

[NH], Br, into the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the compounds **85.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

5 Preparation of the phosphonate ester intermediates 17 in which X is a direct bond and X' is sulfur.

Schemes **87** and **88** illustrate the preparation of the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled with the amine **33.1** to afford the amide **87.1**. The product is then converted, as described in Scheme **49**, into the diamide **87.2**.

The reactions shown in Scheme **87** illustrate the preparation of the compounds **87.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **88** depicts the conversion of the compounds **87.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **87.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X and X' are sulfur.

Schemes **89** and **90** illustrate the preparation of the phosphonate esters **17** in which X and X' are sulfur. As shown in Scheme **89**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the chroman amine **33.1** to give the amide **89.1**. The product is then transformed, as described in Scheme **49**, into the diamide **89.2**.

The reactions shown in Scheme **89** illustrate the preparation of the compounds **89.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **90** depicts the conversion of the compounds **89.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X and X' are sulfur. In this procedure, the compounds **89.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X is sulfur and X' is a direct bond.

Schemes 91 and 92 illustrate the preparation of the phosphonate esters 17 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1, which is an intermediate compound in the conversion of the lactone 83.1 into the diamide 83.2, (Scheme 83), is coupled, as described in Scheme 1, with the chroman amine 33.1 to afford the amide 91.2. The product is then converted, as described in Scheme 49, into the diamide 91.3.

The reactions shown in Scheme 91 illustrate the preparation of the compounds 91.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 92 depicts the conversion of the compounds 91.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 17 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 91.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 17.

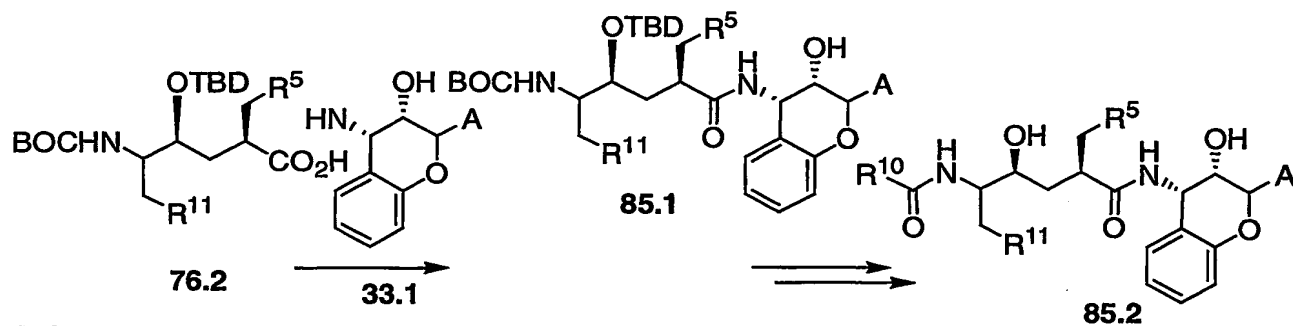
Preparation of the phosphonate ester intermediates 18 in which X and X' are direct bonds.

Schemes 93 and 94 illustrate the preparation of the phosphonate esters 18 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to afford the amide 93.1. The product is then converted, as described in Scheme 49, into the diamide 93.2.

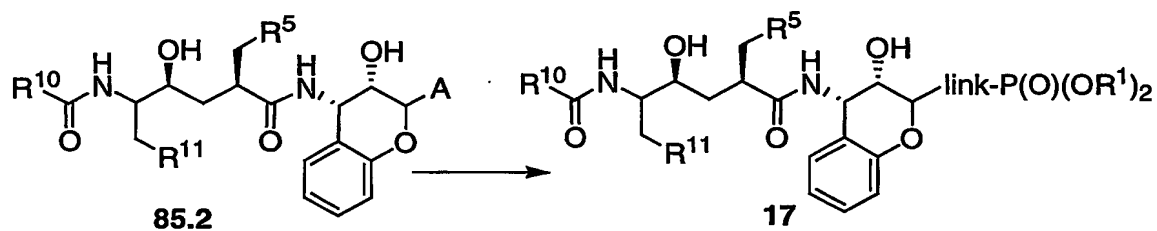
The reactions shown in Scheme 93 illustrate the preparation of the compounds 93.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 94 depicts the conversion of the compounds 93.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X and X' are direct bonds. In this procedure, the compounds 93.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 18.

Preparation of the phosphonate ester intermediates 18 in which X and X' are sulfur.

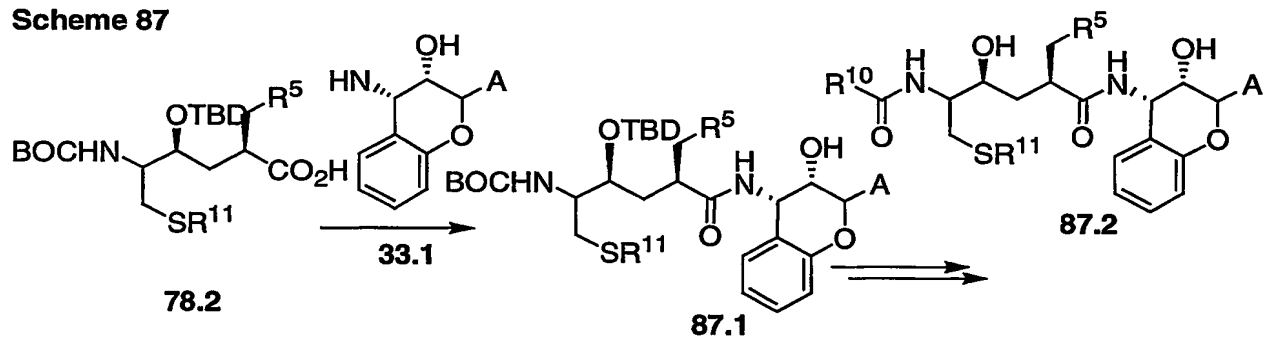
Scheme 85



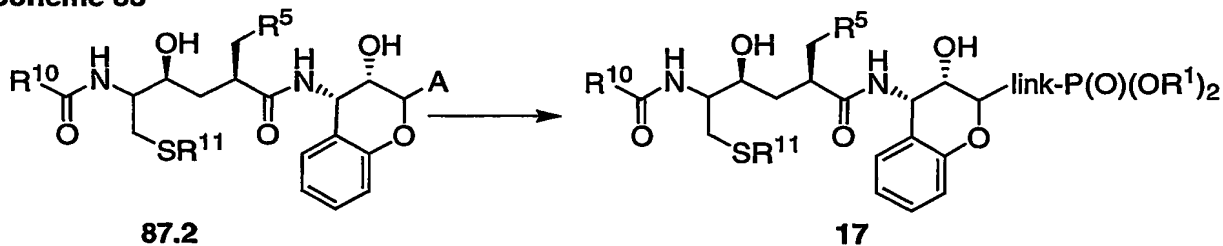
Scheme 86



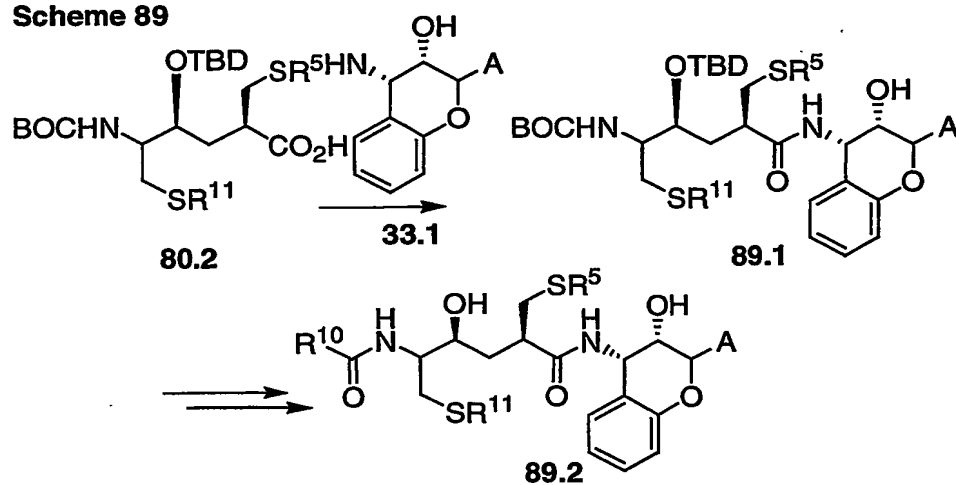
Scheme 87



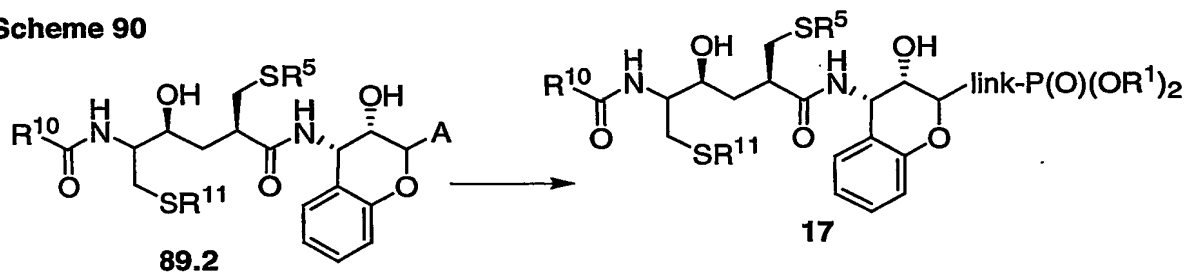
Scheme 88



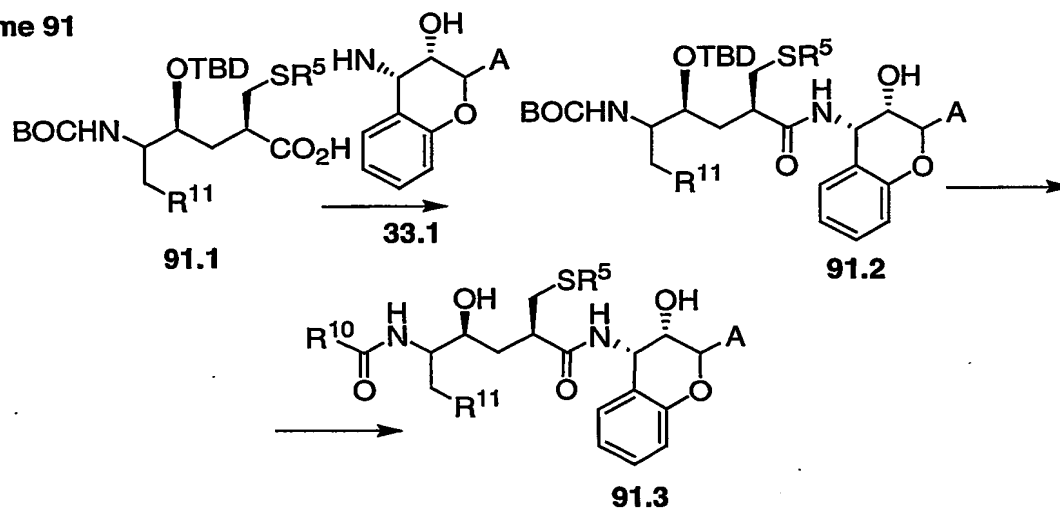
Scheme 89



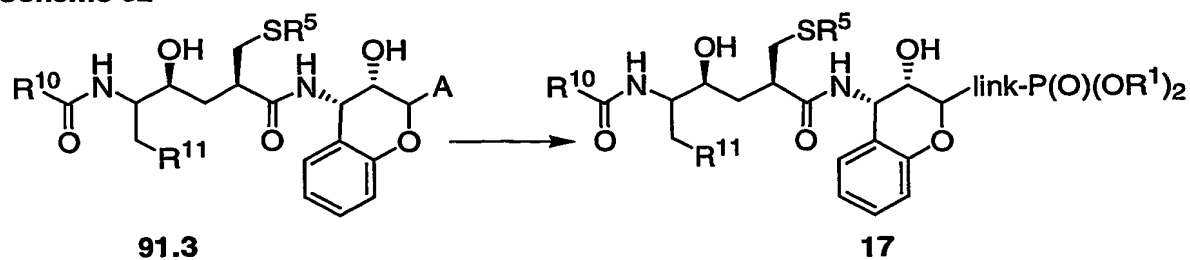
Scheme 90

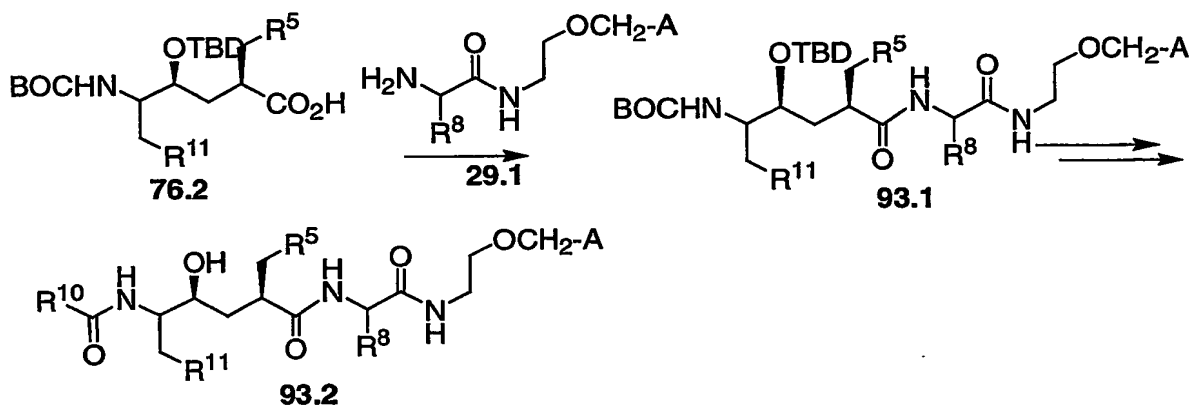
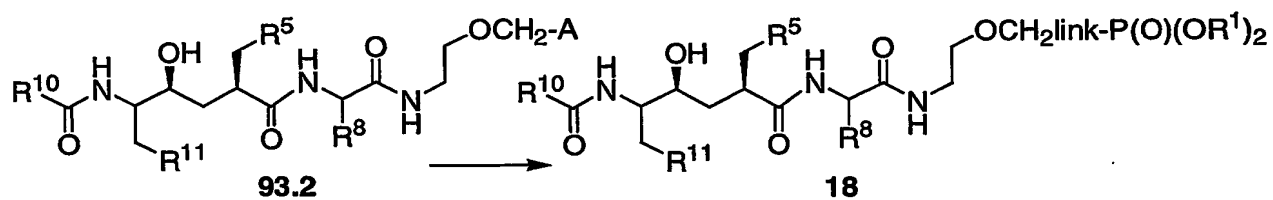
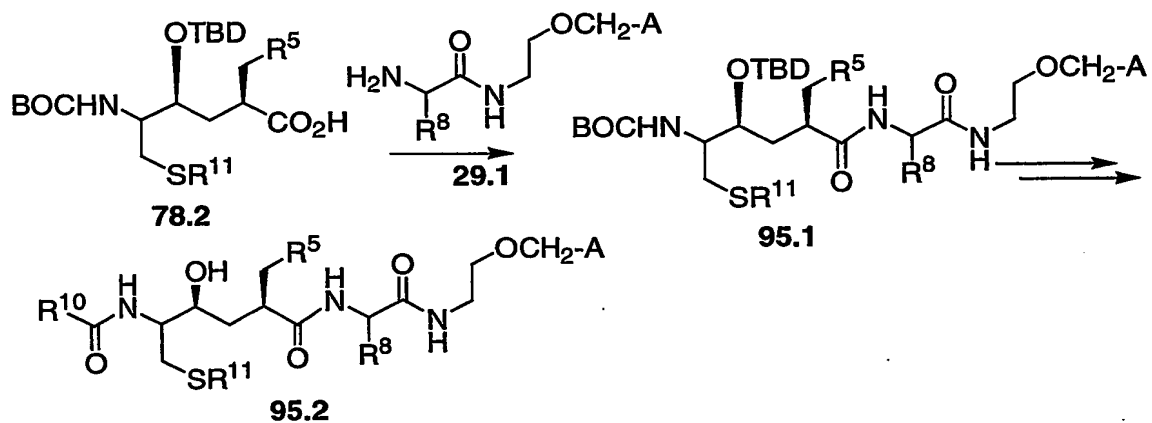
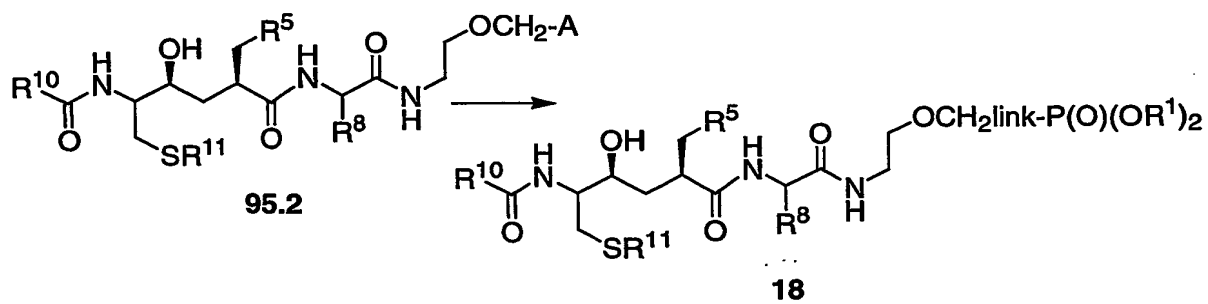


Scheme 91



Scheme 92



Scheme 93**Scheme 94****Scheme 95****Scheme 96**

Schemes 97 and 98 illustrate the preparation of the phosphonate esters 18 in which X and X' are sulfur. As shown in Scheme 97, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to give the amide 97.1. The product is then transformed, as described in Scheme 49, into the diamide 97.2.

- 5 The reactions shown in Scheme 97 illustrate the preparation of the compounds 97.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 98 depicts the conversion of the compounds 97.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X and X' are sulfur. In this procedure, the compounds 97.2 are converted, using the procedures described below, Schemes 133 - 197,
10 into the compounds 18.

Preparation of the phosphonate ester intermediates 18 in which X is sulfur and X' is a direct bond.

- Schemes 99 and 100 illustrate the preparation of the phosphonate esters 18 in which X is
15 sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the ethanolamine derivative 29.1 to afford the amide 99.1. The product is then converted, as described in Scheme 49, into the diamide 99.2.

- The reactions shown in Scheme 99 illustrate the preparation of the compounds 99.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH],
20 [NH], Br. Scheme 100 depicts the conversion of the compounds 99.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 18 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 99.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 18.

- 25 **Preparation of the phosphonate ester intermediates 19 in which X and X' are direct bonds.**

Schemes 101 and 102 illustrate the preparation of the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in

Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 101.1. The product is then converted, as described in Scheme 49, into the diamide 101.2.

The reactions shown in Scheme 101 illustrate the preparation of the compounds 101.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

5 [SH], [NH], Br. Scheme 102 depicts the conversion of the compounds 101.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X and X' are direct bonds. In this procedure, the compounds 101.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

10 **Preparation of the phosphonate ester intermediates 19 in which X is a direct bond and X' is sulfur.**

Schemes 103 and 104 illustrate the preparation of the phosphonate esters 19 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 1, with the amine 37.1 to afford the amide 103.1. The product is then

15 converted, as described in Scheme 49, into the diamide 103.2.

The reactions shown in Scheme 103 illustrate the preparation of the compounds 103.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

[SH], [NH], Br. Scheme 104 depicts the conversion of the compounds 103.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is a direct bond and X' is

20 sulfur. In this procedure, the compounds 103.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 19.

Preparation of the phosphonate ester intermediates 19 in which X and X' are sulfur.

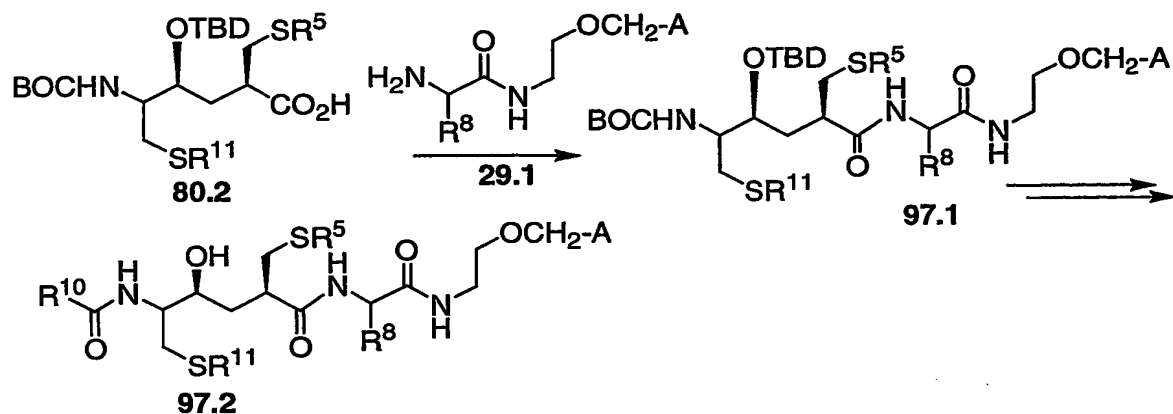
Schemes 105 and 106 illustrate the preparation of the phosphonate esters 19 in which X and

25 X' are sulfur. As shown in Scheme 105, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to give the amide 105.1. The product is then transformed, as described in Scheme 49, into the diamide 105.2.

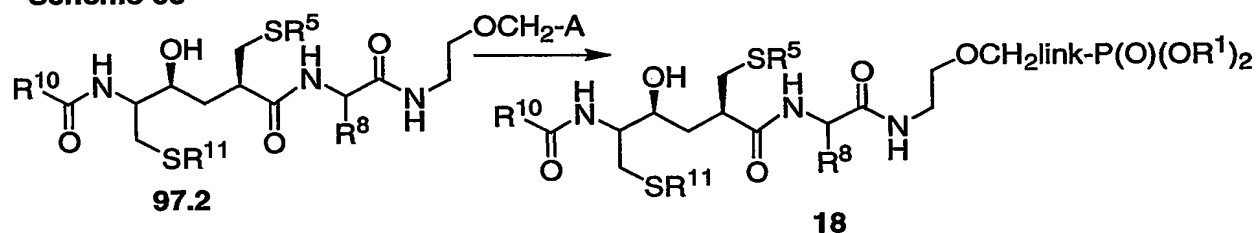
The reactions shown in Scheme 105 illustrate the preparation of the compounds 105.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

[SH], [NH], Br. Scheme **106** depicts the conversion of the compounds **105.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are sulfur. In this procedure, the compounds **105.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19**.

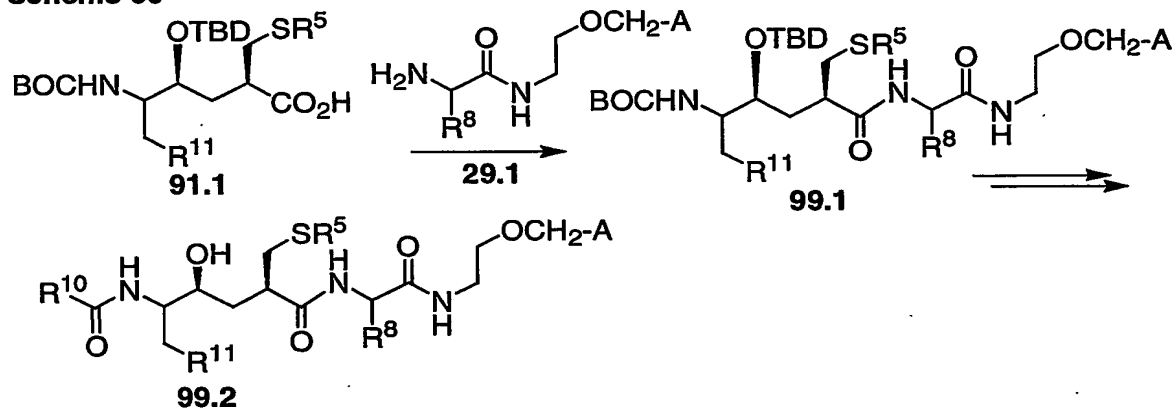
Scheme 97



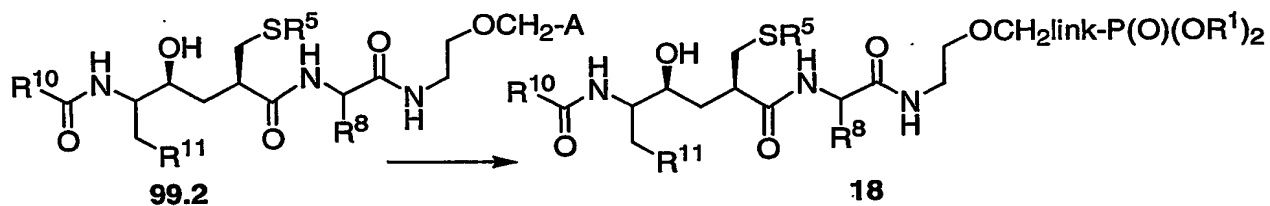
Scheme 98



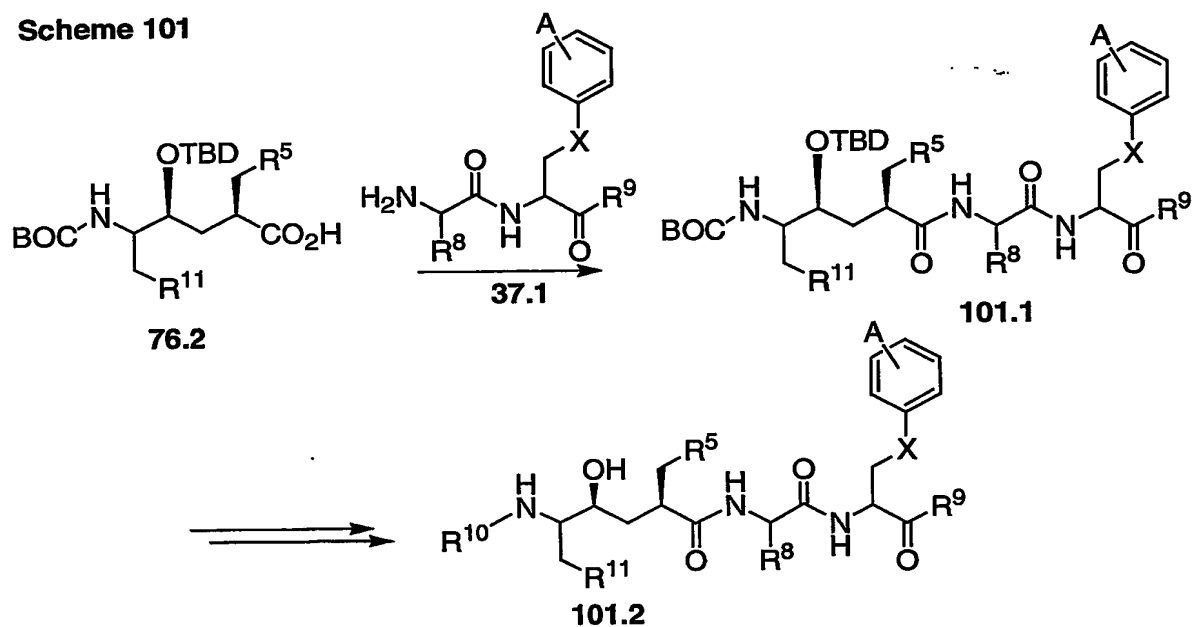
Scheme 99



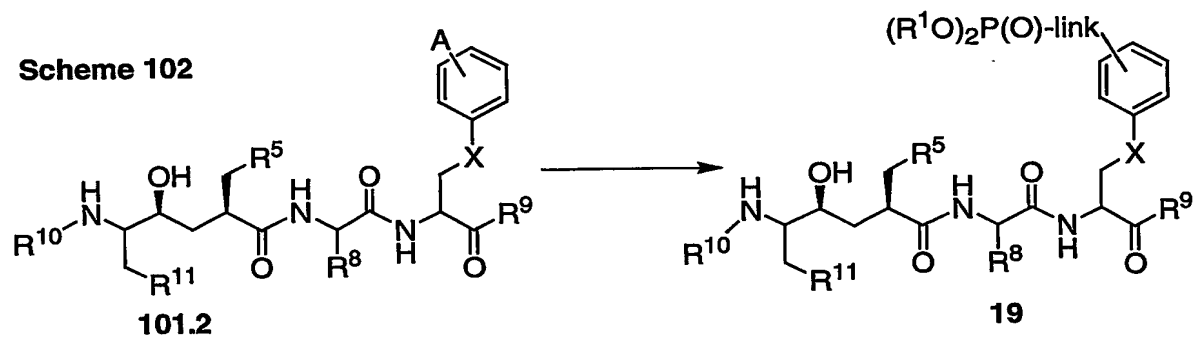
Scheme 100



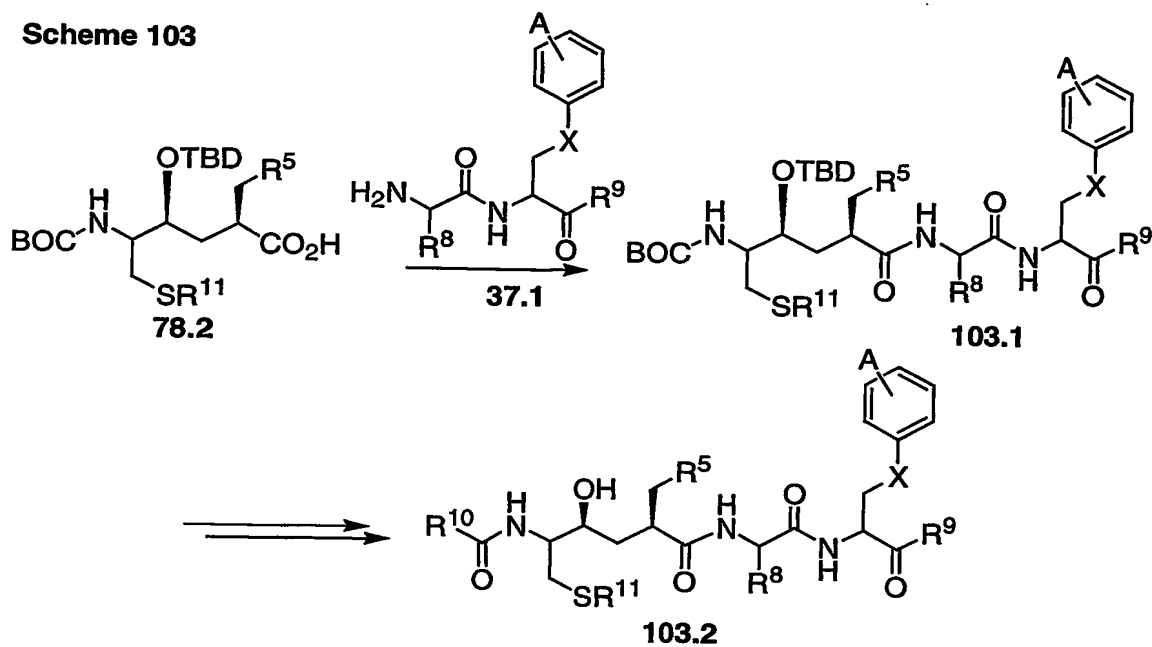
Scheme 101



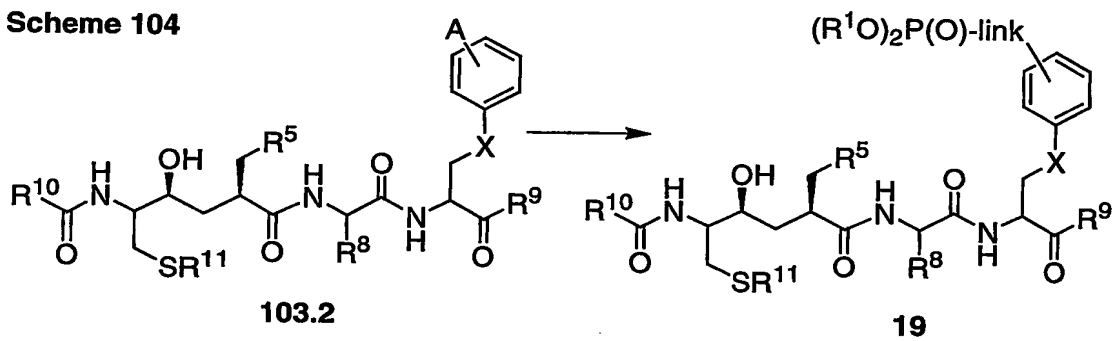
Scheme 102



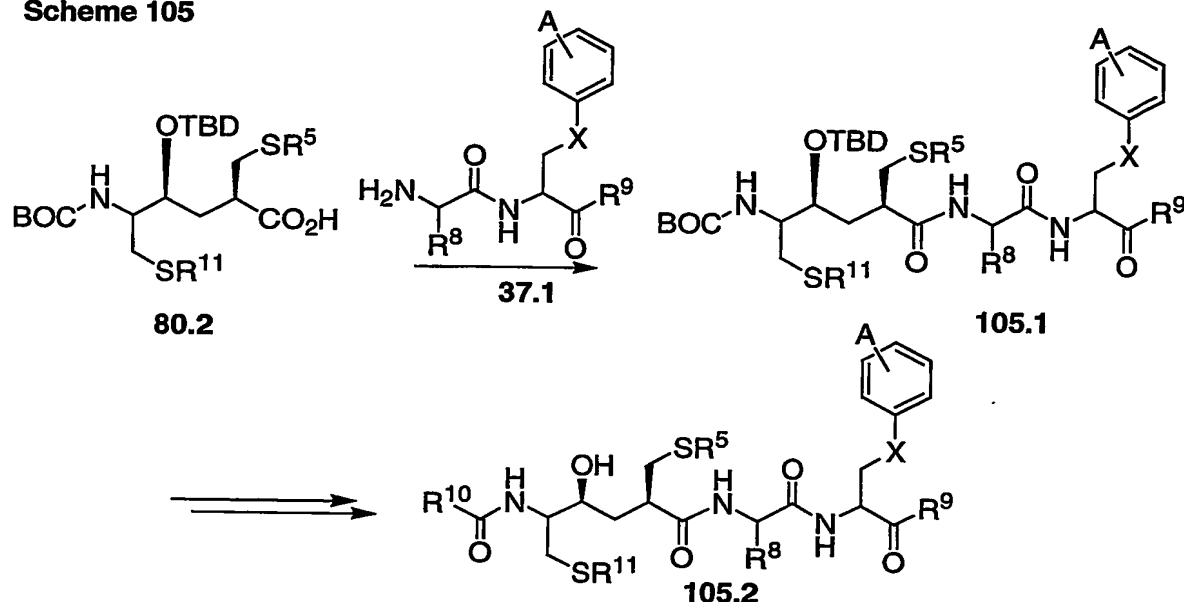
Scheme 103



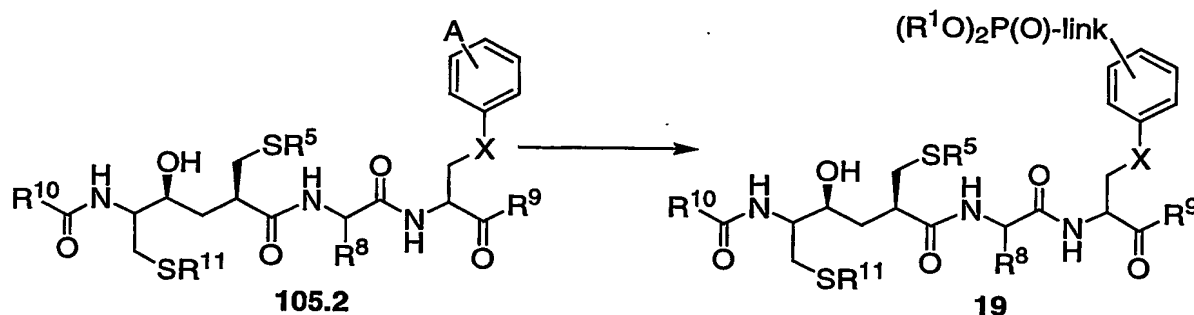
Scheme 104



Scheme 105



Scheme 106



Preparation of the phosphonate ester intermediates 19 in which X is sulfur and X' is a direct bond.

- 5 Schemes 107 and 108 illustrate the preparation of the phosphonate esters 19 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the phenylalanine derivative 37.1 to afford the amide 107.1. The product is then converted, as described in Scheme 49, into the diamide 107.2.

- 10 The reactions shown in Scheme 107 illustrate the preparation of the compounds 107.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 108 depicts the conversion of the compounds 107.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 19 in which X is sulfur and X' is a direct

bond. In this procedure, the compounds **107.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are direct bonds.

Schemes **109** and **110** illustrate the preparation of the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **109.1**. The product is then converted, as described in Scheme **49**, into the diamide **109.2**.

- 10 The reactions shown in Scheme **109** illustrate the preparation of the compounds **109.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **110** depicts the conversion of the compounds **109.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the compounds **109.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is a direct bond and X' is sulfur.

- 20 Schemes **111** and **112** illustrate the preparation of the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **41.1** to afford the amide **111.1**. The product is then converted, as described in Scheme **49**, into the diamide **111.2**.

- 25 The reactions shown in Scheme **111** illustrate the preparation of the compounds **111.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **112** depicts the conversion of the compounds **111.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **111.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are sulfur.

Schemes 113 and 114 illustrate the preparation of the phosphonate esters 20 in which X and X' are sulfur. As shown in Scheme 113, the carboxylic acid 80.2 is coupled, as described in Scheme 1, with the tert. butylamine derivative 41.1 to give the amide 113.1. The product is then transformed, as described in Scheme 49, into the diamide 113.2.

The reactions shown in Scheme 113 illustrate the preparation of the compounds 113.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 114 depicts the conversion of the compounds 113.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X and X' are sulfur. In this procedure, the compounds 113.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

Preparation of the phosphonate ester intermediates 20 in which X is sulfur and X' is a direct bond.

Schemes 115 and 116 illustrate the preparation of the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the tert. butylamine derivative 41.1 to afford the amide 115.1. The product is then converted, as described in Scheme 49, into the diamide 115.2.

The reactions shown in Scheme 115 illustrate the preparation of the compounds 115.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 116 depicts the conversion of the compounds 115.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 20 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 115.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 20.

Preparation of the phosphonate ester intermediates 21 in which X and X' are direct bonds.

Schemes 117 and 118 illustrate the preparation of the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 1, with the decahydroisoquinoline derivative 45.1 to afford the amide 117.1. The product is then converted, as described in Scheme 49, into the diamide 117.2.

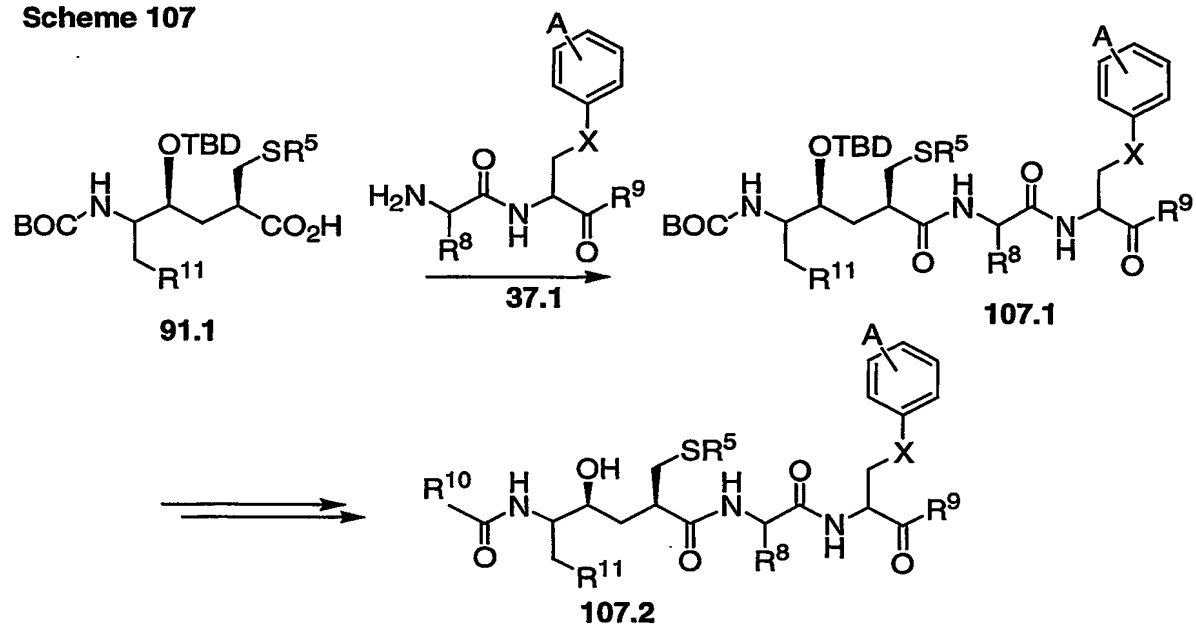
- 5 The reactions shown in Scheme 117 illustrate the preparation of the compounds 117.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 118 depicts the conversion of the compounds 117.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are direct bonds. In this procedure, the compounds 117.2 are converted, using the procedures described below,
- 10 Schemes 133 - 197, into the compounds 21.

Preparation of the phosphonate ester intermediates 21 in which X is a direct bond and X' is sulfur.

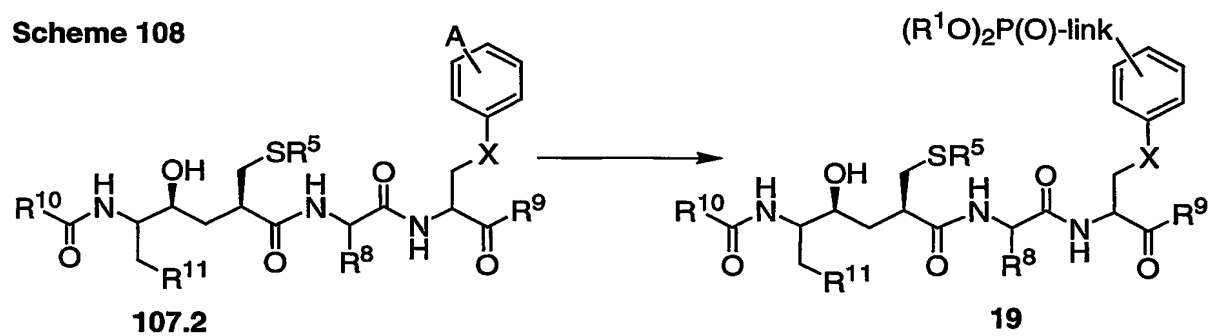
- 15 Schemes 119 and 120 illustrate the preparation of the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 119.1. The product is then converted, as described in Scheme 49, into the diamide 119.2.

- 20 The reactions shown in Scheme 119 illustrate the preparation of the compounds 119.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 120 depicts the conversion of the compounds 119.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is a direct bond and X' is sulfur. In this procedure, the compounds 119.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

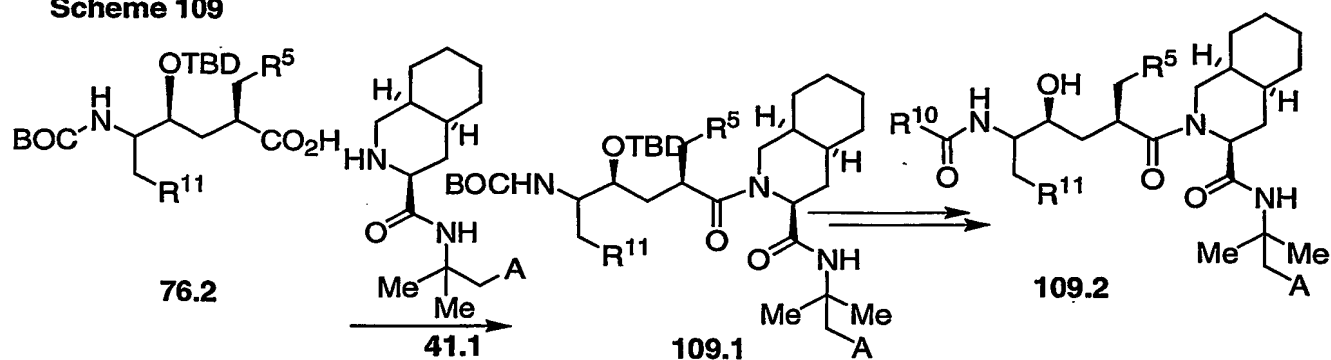
Scheme 107



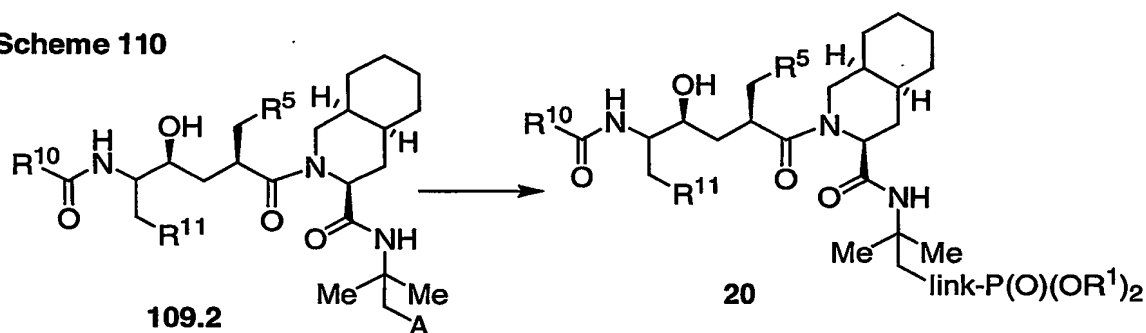
Scheme 108



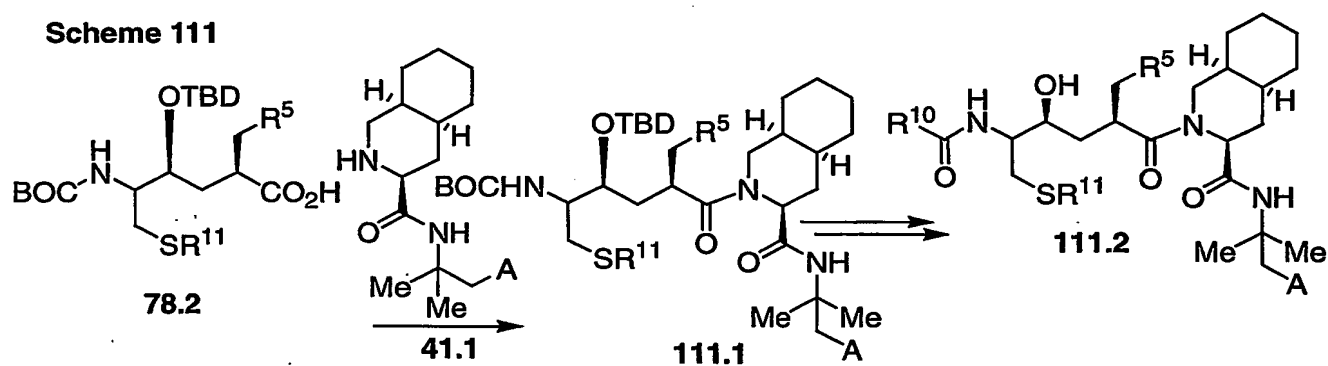
Scheme 109



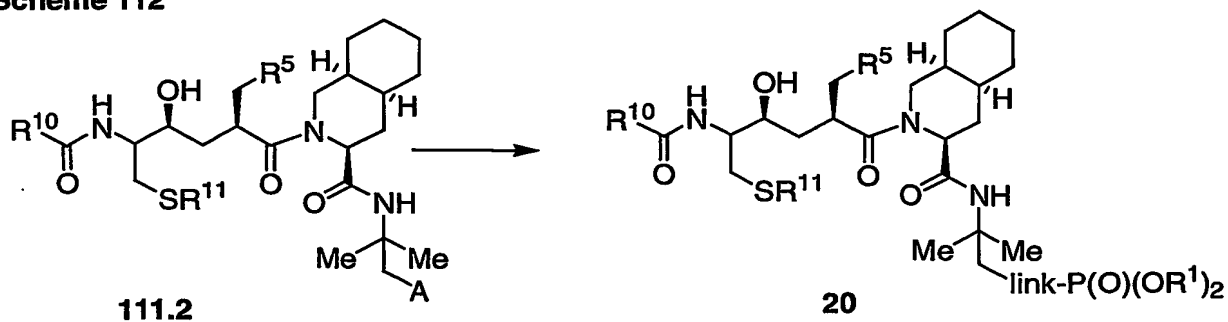
Scheme 110



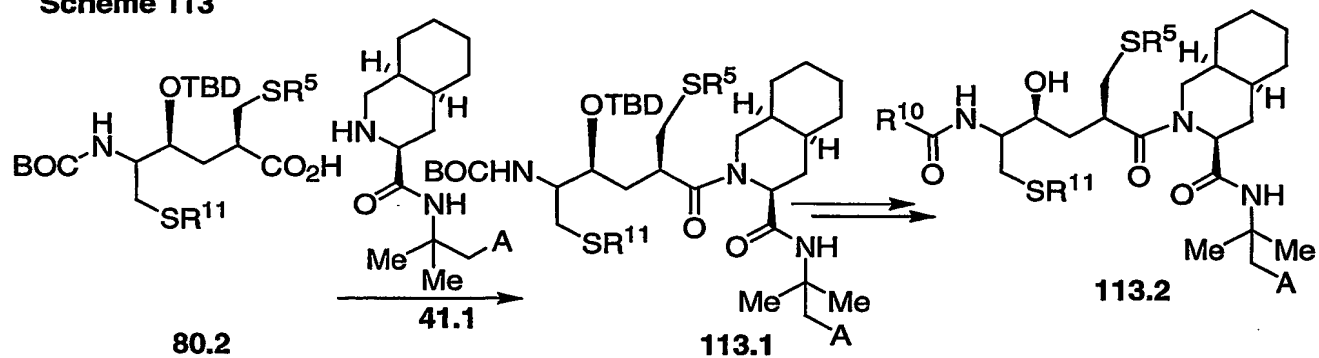
Scheme 111



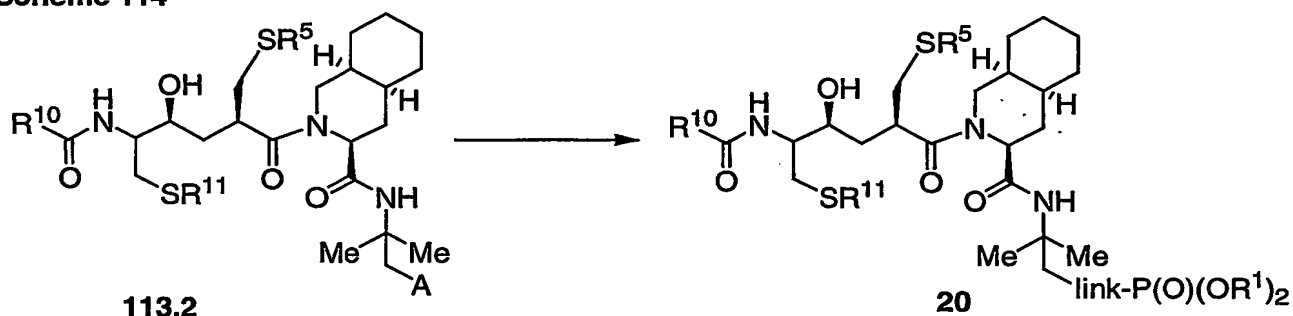
Scheme 112



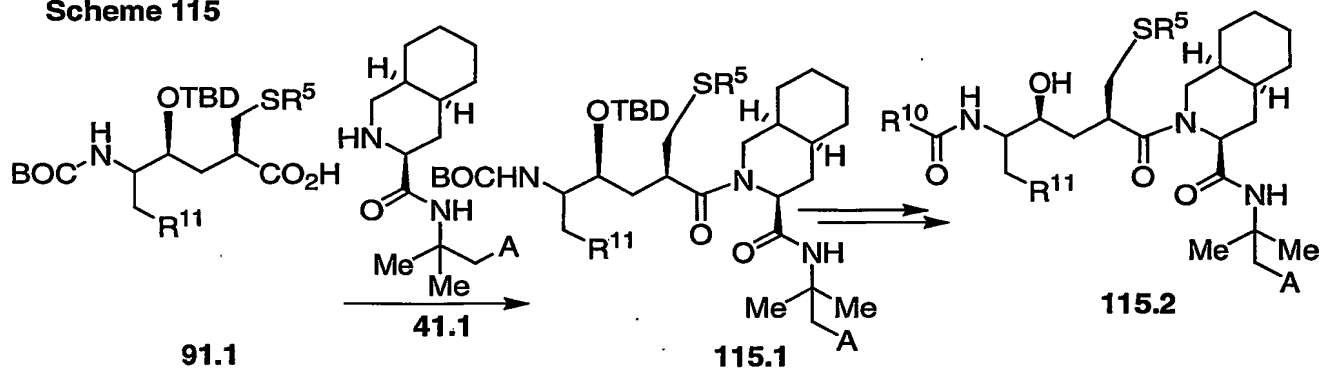
Scheme 113



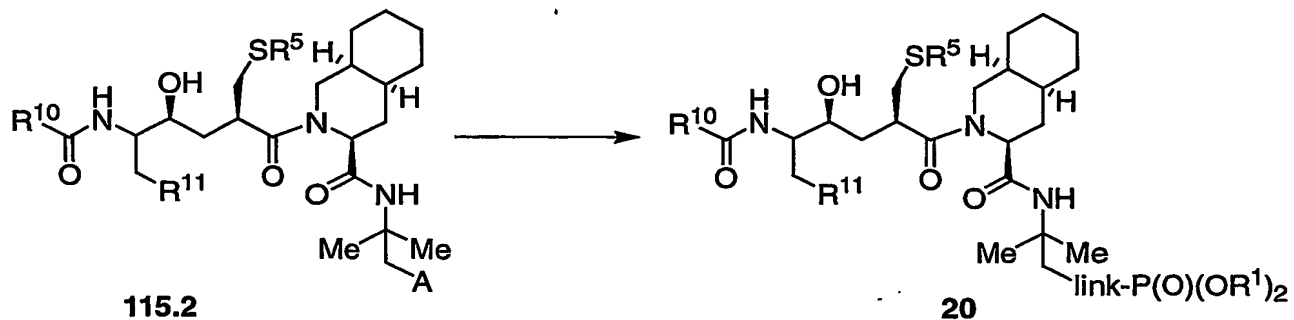
Scheme 114



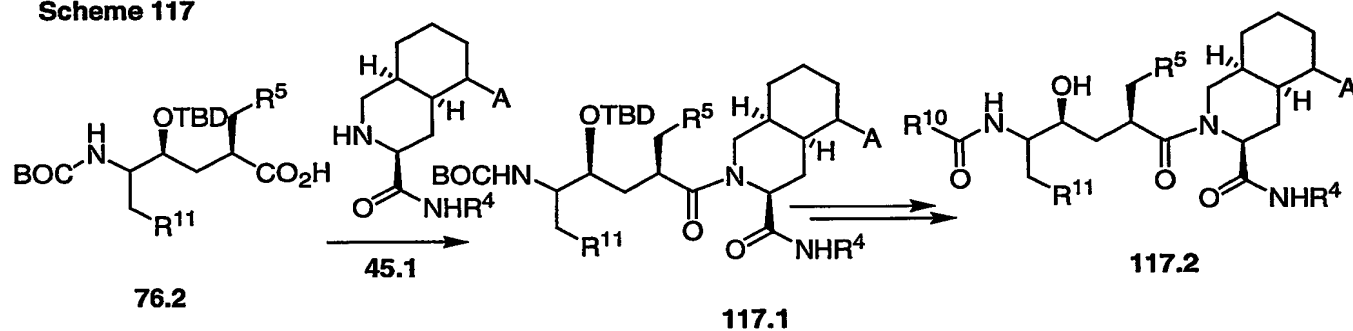
Scheme 115



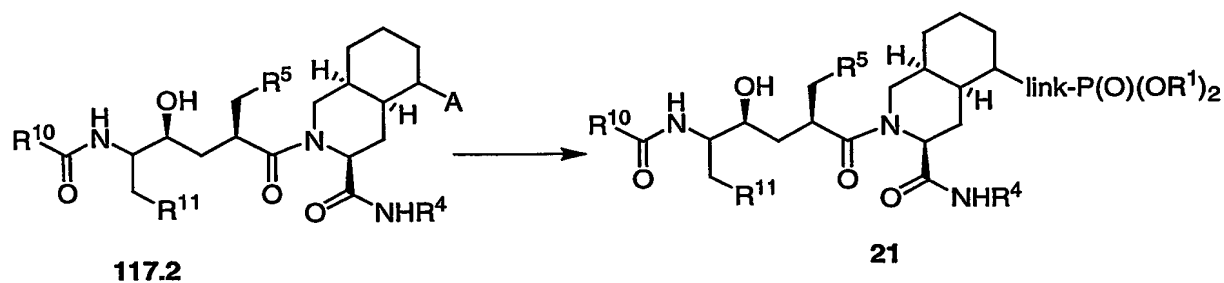
Scheme 116



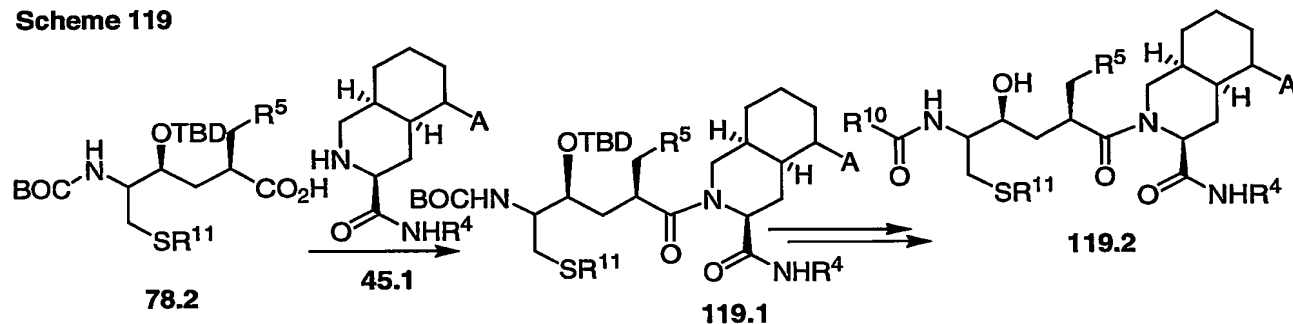
Scheme 117



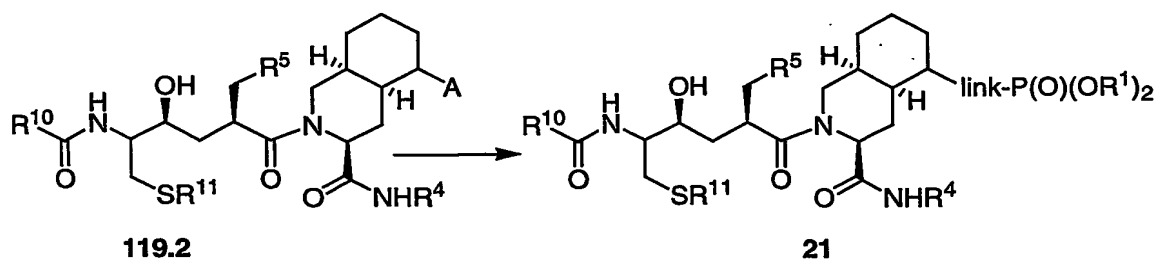
Scheme 118



Scheme 119



Scheme 120



Preparation of the phosphonate ester intermediates 21 in which X and X' are sulfur.

- 5 Schemes 121 and 122 illustrate the preparation of the phosphonate esters 21 in which X and X' are sulfur. As shown in Scheme 121, the carboxylic acid 80.2 is coupled with the amine

45.1 to give the amide 121.1. The product is then transformed, as described in Scheme 49, into the diamide 121.2.

The reactions shown in Scheme 121 illustrate the preparation of the compounds 121.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 122 depicts the conversion of the compounds 121.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are sulfur. In this procedure, the compounds 121.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

10 **Preparation of the phosphonate ester intermediates 21 in which X is sulfur and X' is a direct bond.**

Schemes 123 and 124 illustrate the preparation of the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 123.1. The product is then converted, as described in Scheme 49, into the diamide 123.2.

The reactions shown in Schemes 123 illustrate the preparation of the compounds 123.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 124 depicts the conversion of the compounds 123.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 123.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

Preparation of the phosphonate ester intermediates 22 in which X and X' are direct bonds.

Schemes 125 and 126 illustrate the preparation of the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 125.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 125.2. The latter compound is then

coupled with the carboxylic acid **125.3** to produce the amide **125.4**. The preparation of the carboxylic acid reactant **125.3** is described in Scheme **191**.

The reactions shown in Scheme **125** illustrate the preparation of the compounds **125.4** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **126** depicts the conversion of the compounds **125.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22** in which X and X' are direct bonds. In this procedure, the compounds **125.4** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**

10 Preparation of the phosphonate ester intermediates 22 in which X is a direct bond and X' is sulfur.

Schemes **127** and **128** illustrate the preparation of the phosphonate esters **22** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **5** with the amine **1.6**, to afford the amide **127.1**. The BOC protecting group is then removed, as described in Scheme **49**, to yield the amine **127.2**. The latter compound is then coupled, as described in Scheme **1**, with the carboxylic acid **125.3** to produce the amide **127.3**.

The reactions shown in Scheme **127** illustrate the preparation of the compounds **127.3** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme **128** depicts the conversion of the compounds **127.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22**, in which X is a direct bond and X' is sulfur. In this procedure, the compounds **127.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**.

25 Preparation of the phosphonate ester intermediates 22 in which X and X' are sulfur.

Schemes **129** and **130** illustrate the preparation of the phosphonate esters **22** in which X and X' are sulfur. As shown in Scheme **129**, the carboxylic acid **80.2** is coupled, as described in Scheme **5**, with the amine **1.6**, to afford the amide **129.1**. The BOC protecting group is then

removed, as described in Scheme 49, to yield the amine 129.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 129.3.

The reactions shown in Scheme 129 illustrate the preparation of the compounds 129.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

5 [SH], [NH], Br. Scheme 130 depicts the conversion of the compounds 129.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X and X' are sulfur. In this procedure, the compounds 129.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

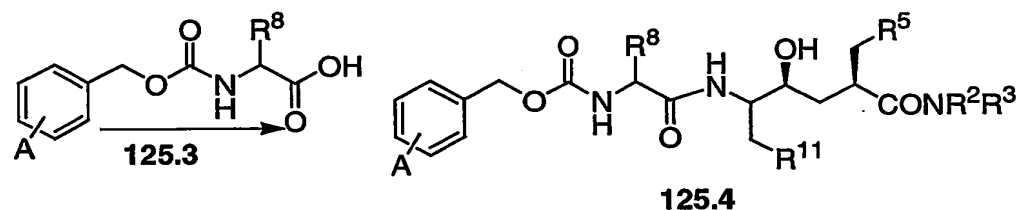
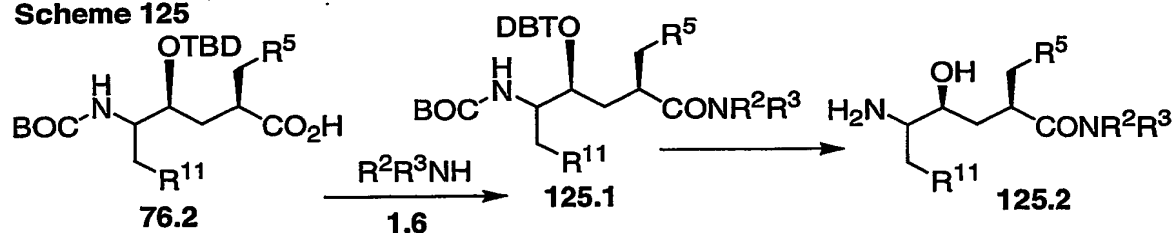
10 **Preparation of the phosphonate ester intermediates 22 in which X is sulfur and X' is a direct bond.**

Schemes 131 and 132 illustrate the preparation of the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 131.1. The BOC protecting
15 group is then removed, as described in Scheme 49, to yield the amine 131.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 131.3.

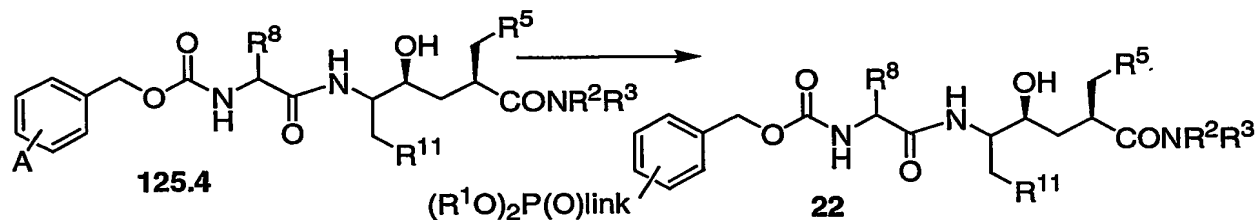
The reactions shown in Scheme 131 illustrate the preparation of the compounds 131.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],
20 [SH], [NH], Br. Scheme 132 depicts the conversion of the compounds 131.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 131.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

25

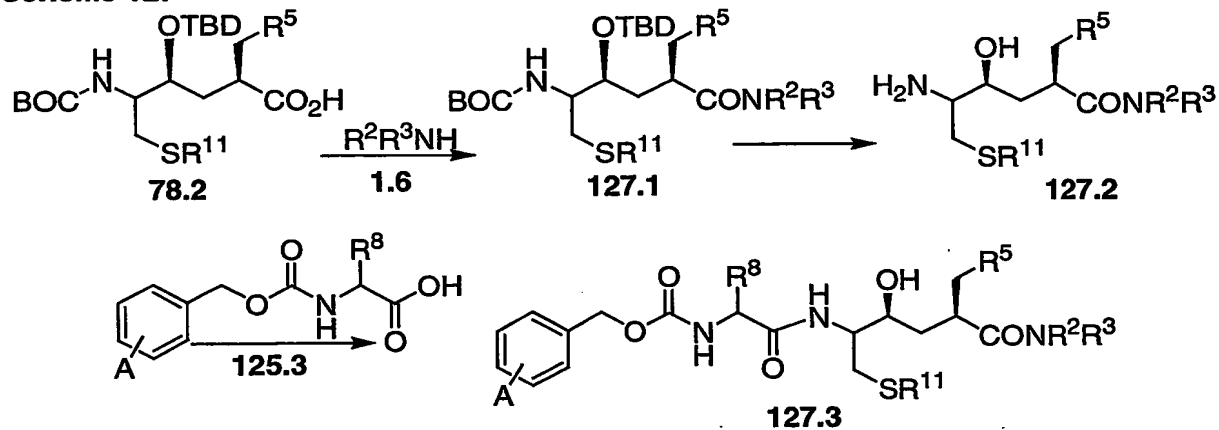
Scheme 125



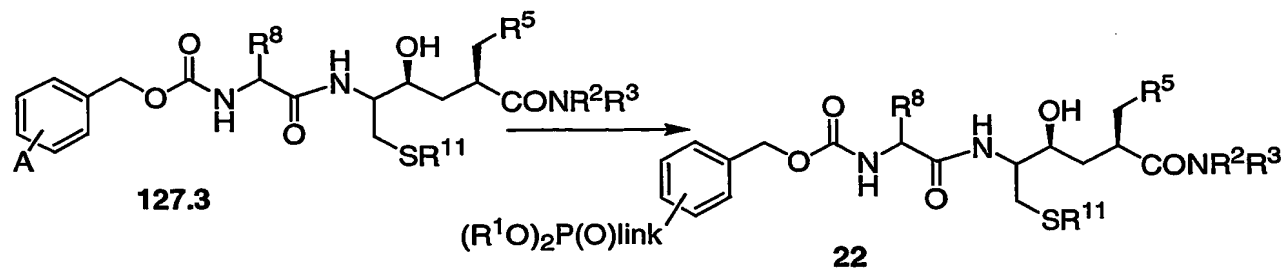
Scheme 126

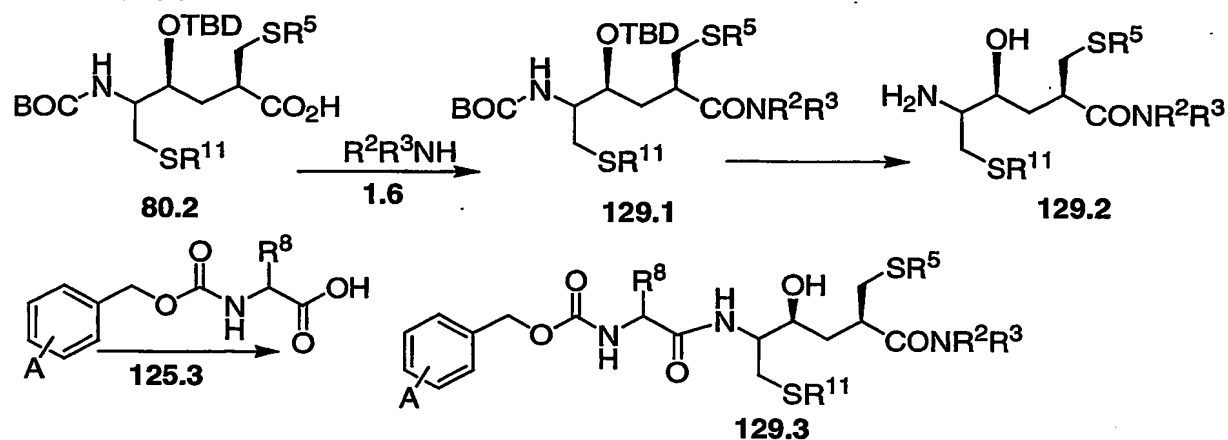
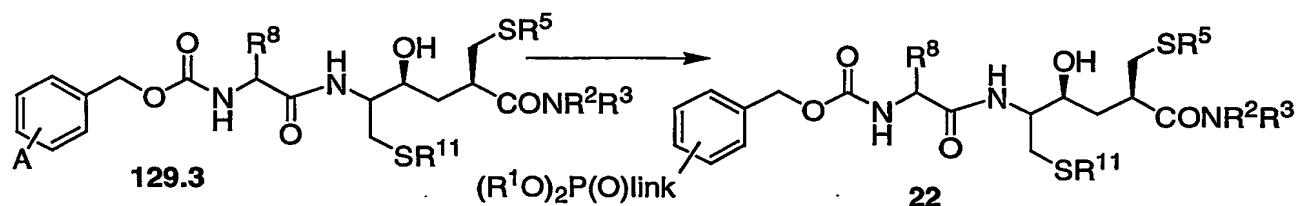
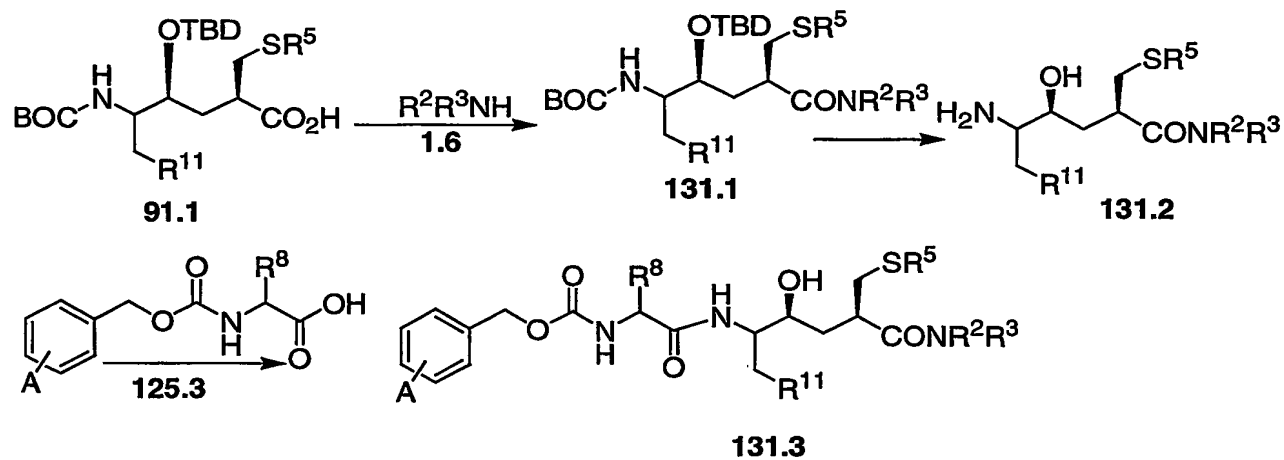
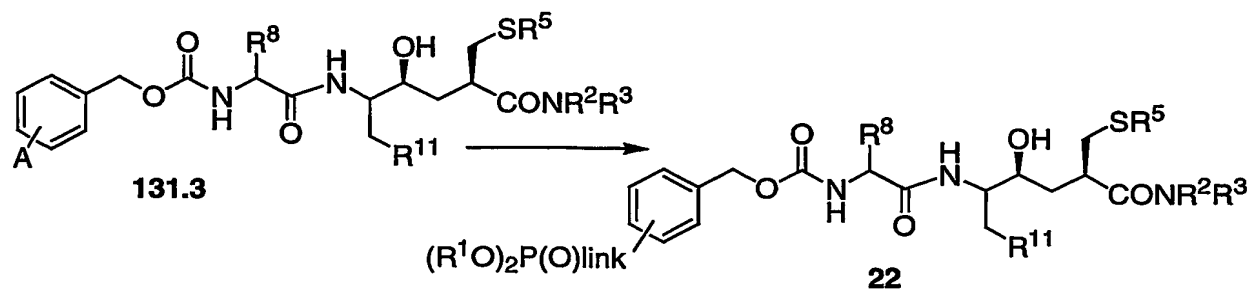


Scheme 127



Scheme 128



Scheme 129**Scheme 130****Scheme 131****Scheme 132**

Preparation of aminoindanol derivatives 1.2 incorporating phosphonate moieties.

Scheme 133 illustrates the preparation of variously substituted derivatives of 3-amino-indan-1,2-diol, the preparation of which is described in J. Med. Chem., 1991, 34, 1228. The
5 alcohols, thiols, amines and bromo compounds shown in Scheme 133 can then be transformed into phosphonate-containing reactants 1.2, as described below, (Schemes 134 - 137). The reactants 1.2 are employed in the preparation of the phosphonate esters 1 and 16.

In order to effect changes to the 1-substituent, the starting material 133.1 is transformed into the protected compound 133.2. For example, the aminoalcohol 133.1 is treated with 2-
10 methoxypropene in the presence of an acid catalyst, such as p-toluenesulfonic acid, in a solvent such as tetrahydrofuran, as described in WO9628439, to afford the acetonide-protected product 133.2.

The amino group present in 133.2 is protected to afford the intermediate 133.3, in which R¹² is a protecting group, stable to the subsequent reactions. For example, R¹² can be
15 carbobenzyloxy (cbz), tert-butoxycarbonyl (BOC) and the like, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309.

The free hydroxyl group present in the N-protected acetonide 133.3 is then converted into a suitable leaving group, such as, for example, trifluoromethylsulfonyloxy, p-toluenesulfonyloxy
20 or, preferably, methanesulfonyloxy. This transformation is effected by treatment of 133.3 with a slight molar excess of the corresponding acid chloride or anhydride, in the presence of an organic base.

For example, treatment of 133.3 with methanesulfonyl chloride and pyridine in dichloromethane at ambient temperature affords the mesylate 133.4.

25 The α -mesylate group in the product 133.4 is then subjected to displacement reactions with nitrogen, sulfur or oxygen nucleophiles, to effect introduction of the various heteroatoms with inversion of stereochemistry.

For example, the mesylate 133.4 is reacted with a nitrogen nucleophile such as potassium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic
30 Transformations, by R. C. Larock, VCH, p. 399, to afford the amine 133.9.

Preferably, the mesylate 133.4 is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **133.5**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the β -amine **133.9**.

- 5 The mesylate **133.4** is treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate group, followed by mild basic hydrolysis, for example by treatment with aqueous sodium bicarbonate or aqueous ammonia, to afford the β -thiol **133.12**.
- 10 Preferably, the mesylate **133.4** is reacted with one molar equivalent of potassium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **133.8**. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the β -thiol **133.12**.
- 15 The mesylate **133.4** is transformed into the β -carbinol **133.7**, by treatment with an oxygen nucleophile. Conversion of sulfonate esters and related compounds to the corresponding carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 481. For example, the mesylate can be reacted with potassium superoxide, in the presence of a crown ether such as 18-crown-6, as described in Tet. Lett., 3183, 1975, to
- 20 afford the β -carbinol **133.7**.
- The carbinol **133.3** is also transformed into the β -bromo compound **133.6**. Methods for the conversion of carbinols to bromo compounds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 356.
- For example, the α -carbinol **133.3** is reacted with hexabromoethane and triphenylphosphine, in
- 25 an aprotic solvent such as ethyl acetate, as described in Syn., 139, 1983, to afford the β -bromo compound **133.6**.
- Using the above described procedures for the conversion of the α -carbinol **133.3** into the β -oriented amine **133.9**, thiol **133.12** and bromo compound **133.6**, the β -carbinol **133.7** is transformed into the α -oriented amine or thiol **133.11** or the bromo compound **133.10**.

Schemes 134 - 137 illustrate the preparation of aminoindanol derivatives incorporating the group link-P(O)(OR¹)₂, derived from the intermediates whose syntheses are described above (Scheme 133).

- 5 Scheme 134 depicts the preparation of phosphonate esters linked to the aminoindanol nucleus by means of a carbon chain and a heteroatom O, S or N. In this procedure, the hetero-substituted indanol 134.1 is reacted with a bromoalkylphosphonate 134.2, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for
10 example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80°C to afford the displacement products 134.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, by removal of the group R¹²,
15 then affords the amine 134.4.
- For example, the β-thiol 133.12 is reacted with an equimolar amount of dialkyl 4-bromobutyl phosphonate 134.5, the preparation of which is described in Synthesis, 1999, 9, 909, in dimethylformamide containing excess potassium carbonate, at ca 60°C to afford the thioether phosphonate product 134.6. Deprotection then affords the amine 134.7.
- 20 Using the above procedures, but employing, in place of the thiol 133.12, different carbinols, thiols or amines 134.1, and/or different bromoalkylphosphonates 134.2, the corresponding products 134.4 are obtained.

- Scheme 135 illustrates the preparation of aminoindanol derivatives in which the phosphonate ester group is attached by means of a nitrogen atom and a carbon chain. In this method, the aminoindanol 135.1 is reacted with a formyl-substituted phosphonate ester, utilizing a
25 reductive amination procedure. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 135.1 and the aldehyde
30 component 135.2 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 135.3. Deprotection, by removal of the R¹² group, then affords the amine 135.4.

For example, equimolar amounts of the amine **133.11** and a dialkylformylphosphonate **135.5**, prepared as described in US 3784590, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the product **135.6** which is then deprotected to produce the amine **135.7**.

- 5 Using the above procedures, but employing, in place of the α -amine **133.11**, the β -amine **133.9**, and/or different formyl-substituted phosphonates **135.2**, the corresponding products **135.4** are obtained.

- 10 Scheme **136** depicts the preparation of aminoindanol phosphonates in which the phosphonate moiety is attached to the nucleus by means of a heteroatom and one carbon. In this procedure, a carbinol, thiol or amine **136.1** is reacted with a dialkyl trifluoromethylsulfonyloxy phosphonate **136.2**, in the presence of a suitable base, to afford the alkylation product **136.3**. Deprotection of the product **136.3** then yields the amine **136.4**. The base required for this reaction between **136.1** and **136.2** depends on the nature of the heteroatom X. For example, if
- 15 X is N or S, an excess of inorganic base such as, for example, potassium carbonate, cesium carbonate or the like, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **136.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide, sodium hydride or the like, is employed, in the
- 20 presence of a solvent such as tetrahydrofuran.

- For example, the α -carbinol **133.3** is reacted with one equivalent of lithium hexamethyl disilylazide in tetrahydrofuran, followed by addition of an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **136.5**, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product **136.6**. Deprotection, by removal of the
- 25 R¹² group, then affords the amine **136.7**.

Using the above procedures, but employing, in place of the α -carbinol **133.3**, different carbinols, thiols or amines **136.1**, and /or different dialkyl trifluoromethylsulfonyloxymethyl phosphonates **136.2**, the corresponding products **136.4** are obtained.

- 30 Scheme **137** illustrates the preparation of aminoindanol phosphonate esters in which the phosphonate group is attached directly to the aminoindanol nucleus.

In this procedure, the bromoindanol derivative **137.1** is reacted with a sodium dialkyl phosphite, in a suitable aprotic polar solvent such as dimethyl formamide or N-methylpyrrolidinone. Displacement of the bromo substituent occurs to yield the phosphonate **137.3**. Deprotection, by removal of the R¹² group, then affords the amine **137.4**.

5 For example, equimolar amounts of the α -bromo compound **133.10** and the dialkyl sodium phosphite **137.2**, are dissolved in dimethylformamide and the mixture is heated at ca. 60°C, as described in J. Med. Chem., 35, 1371, 1992, to afford the β -phosphonate **137.5**.

Alternatively, the phosphonate compound **137.5** is obtained by means of an Arbuzov reaction between the bromo compound **133.10** and a trialkyl phosphite P(OR¹)₃. In this procedure, as
10 described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **137.5**. Deprotection of the latter compound affords the amine **137.6**.

Using the above procedures, but employing, in place of the α -bromo compound **133.10**, the β -bromo compound **133.6**, and/or different phosphites **137.2**, the corresponding phosphonates
15 **137.4** are obtained.

Preparation of phenylpropionic acid intermediates 5.1 incorporating phosphonate moieties.

20 Phenylpropionic acid derivatives incorporating the substituent link-P(O)(OR¹)₂ are prepared by the reactions illustrated in Schemes **139-143**, using as starting materials variously substituted phenylpropionic acids. The phenylpropionic acid derivatives **5.1** are employed in the preparation of the phosphonate esters **2** in which X is a direct bond.

A number of the substituted phenylpropionic acids required for the reactions shown in
25 Schemes **139-143** are commercially available; in addition, the syntheses of variously substituted phenylpropionic acids have been reported. For those substituted phenylpropionic acids which are not commercially available, and whose syntheses have not been reported, a number of well-established synthetic routes are available. Representative methods for the synthesis of substituted phenylpropionic acids from commercially available starting materials
30 are shown in Scheme **138**.

For example, variously substituted benzaldehydes **138.1** are subjected to a Wittig reaction with carboethoxymethylenetriphenylphosphorane **138.2**, as described in Ylid Chemistry, by A. W.

Johnson, Academic Press, 1966, p. 132, to afford the corresponding cinnamate esters **138.3**. Equimolar amounts of the reactants **138.1** and **138.2** are heated in an inert solvent such as dioxan or dimethylformamide, at ca 50°C, to afford the product **138.3**. Reduction of the double bond in the product **138.3** then afford the saturated ester **138.6**, (X =H) which upon hydrolysis yields the phenylpropionic acid intermediate **138.10**.

Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 6. Typical of the available reduction methods are catalytic hydrogenation, for example using palladium catalysts, as described in Hydrogenation Methods, by P. N. Rylander, Academic Press, New York, 1985, hydroboration-protonolysis, as described in J. Am. Chem. Soc., 81, 4108, 1959, or diimide reduction, as described in J. Org. Chem., 52, 4665, 1987. The choice of a particular reduction method is made by one skilled in the art, depending on the nature of the substituent groups attached to the cinnamic acid ester **138.3**.

Alternatively, the cinnamic esters **138.3** are obtained by means of a palladium-catalyzed Heck reaction between an appropriately substituted bromobenzene **138.5** and ethyl acrylate **138.4**. In this procedure, a substituted bromobenzene **138.5** is reacted with ethyl acrylate in the presence of a palladium (II) catalyst, as described in J. Med. Chem., 35, 1371, 1992, to afford the cinnamate ester **138.3**. Equimolar amounts of the reactants **138.4** and **138.5** are dissolved in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran, at a temperature of about 60°C, in the presence or ca. 3 mol % of, for example, bis(triphenylphosphine)palladium (II) chloride and triethylamine, to afford the product **138.3**.

Alternatively, the substituted phenylpropionic acid intermediates are obtained from the correspondingly substituted methylbenzenes **138.7**. In this procedure, the methylbenzene **138.7** is subjected to free-radical bromination, for example by reaction with an equimolar amount of N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative **138.8**. The latter compound is then reacted with a salt of an ester of malonic acid, for example the sodium salt of diethyl malonate **138.9**, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 489, to afford the displacement product **138.6**, (X = COOEt). The latter compound is subjected to hydrolysis and decarboxylation, for example by treatment with aqueous alkali or dilute aqueous acid, to afford the phenylpropionic acid **138.10**.

Scheme 139 illustrates the preparation of phosphonate-containing phenylpropionic acids in which the phosphonate moiety is attached to the phenyl ring by means of an aromatic group. In this procedure, the carboxyl group of a bromo-substituted phenylpropionic acid 139.1 is protected. Methods for the protection of carboxylic acids are described, for example, in

- 5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224. The product 139.2 is then subjected to halogen-methyl exchange, for example by reaction with an alkyl lithium, to afford the product 139.3 in which M is Li. The latter compound is subjected to palladium (II) or palladium (0) catalyzed coupling, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.
- 10 Compound 139.3 is first converted into the boronic acid 139.4, by reaction with a trialkyl borate, and the boronic acid product is coupled with a dialkyl bromophenylphosphonate 139.5 to yield the product 139.6. Deprotection then affords the intermediate phosphonate-substituted phenylpropionic acid 139.7.

- For example, 4-bromophenylpropionic acid 139.8, prepared as described in U.S. 4,032,533, is
- 15 converted into the acid chloride, by treatment with thionyl chloride, oxalyl chloride and the like. The acid chloride is then reacted with 3-methyl-3-oxetanemethanol 139.9 (Aldrich), in the presence of a tertiary organic base such as pyridine, in a solvent such as dichloromethane, to afford the ester 139.10. This product is then rearranged by treatment with boron trifluoride etherate in dichloromethane, at about -15°C as described in Protective Groups in Organic
- 20 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 268, to yield the orthoester 139.11, known as an OBO ester. The latter product is then reacted with one molar equivalent of n-butyllithium, in a solvent such as ether, at about -80°C, to afford the lithio derivative, which is reacted with a trialkyl borate, as described in J. Organomet. Chem., 1999, 581, 82, to yield the boronate 139.12. This material is coupled, in the presence of a catalytic
- 25 amount of tetrakis(triphenylphosphine)palladium(0), and an inorganic base such as sodium carbonate, with a dialkyl 4-bromophenylphosphonate 139.13, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 139.14. Deprotection, for example by treatment with aqueous pyridine p-toluenesulfonate, as described in Can. J. Chem., 61, 712, 1983, then affords the carboxylic acid 139.15.

- 30 Using the above procedures, but employing, in place of the 4-bromophenylpropionic acid 139.8, different bromophenylpropionic acids 139.1, and/or different dialkyl bromophenyl phosphonates 139.5, the corresponding products 139.7 are obtained.

Scheme 140 depicts the preparation of phenylpropionic acids in which a phosphonate ester is attached to the phenyl ring by means of a heteroatom. In this procedure, a suitably protected hydroxy, thio or amino-substituted phenyl propionic acid 140.1 is reacted with a derivative of a hydroxymethyl dialkylphosphonate 140.2, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product 140.3. Deprotection then affords the carboxylic acid 140.4.

For example, trichloroethyl 3-hydroxyphenylpropionic acid 140.5, prepared by reaction of 3-hydroxyphenylpropionic acid (Fluka) with trichloroethanol and dicyclohexylcarbodiimide, as described in J. Am. Chem. Soc., 88, 852, 1966, is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 140.6, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product 140.7. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the product 140.7. Removal of the trichloroethyl ester group, for example by treatment with zinc in acetic acid at 0°C, as described in J. Am. Chem. Soc., 88, 852, 1966, then yields the carboxylic acid 140.8. Using the above procedures, but employing, in place of the phenol 140.5, different phenols, thiols or amines 140.1, and/or different phosphonates 140.2, the corresponding products 140.4 are obtained.

Scheme 141 illustrates the preparation of phenylpropionic acids in which a phosphonate moiety is attached by means of a chain incorporating a heteroatom. In this procedure, a carboxyl protected halomethyl substituted phenylpropionic acid 141.1 is reacted with a dialkyl hydroxy, thio or amino-substituted alkylphosphonate 141.2. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 141.2. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed.

For example, 4-bromomethyl phenylpropionic acid, prepared as described in U.S. 4,032,533, is converted into the methoxymethyl ester 141.5, by reaction with methoxymethyl chloride and

triethylamine in dimethylformamide, as described in J. Chem. Soc, 2127, 1965. Equimolar amounts of the ester **141.5** and a dialkyl 2-aminoethyl phosphonate **141.6**, prepared as described in J. Org. Chem., 2000, 65, 676, are reacted in dimethylformamide at ca 80°C, in the presence of potassium carbonate, to afford the displacement product **141.7**. Deprotection, for example by treatment with trimethylsilyl bromide and a trace of methanol, as described in Aldrichimica Acta, 11, 23, 1978, then yields the carboxylic acid **141.8**.

Using the above procedures, but employing, in place of the amine **141.6**, different amines, alcohols or thiols **141.2** and/or different halomethyl-substituted phenylpropionic acids **141.1**, the corresponding products **141.4** are obtained.

Scheme 142 illustrates the preparation of phosphonate esters attached to the phenyl ring by means of an oxygen or sulfur link, by means of a Mitsunobu reaction. In this procedure, a protected hydroxy- or thio-substituted phenylpropionic acid **142.1** is reacted with a dialkyl hydroxyalkyl phosphonate **142.2**. The condensation reaction between **142.1** and **142.2** is effected in the presence of a triaryl phosphine and diethyl azodicarboxylate, as described in Org. React., 1992, 42, 335. The product **142.3** is then deprotected to afford the carboxylic acid **142.4**.

For example, 3-mercaptophenylpropionic acid (Apin Chemicals) is converted into the tert. butyl ester **142.5**, by treatment with carbonyl diimidazole, tert. butanol and

diazabicycloundecene, as described in Synthesis, 833, 1982. The ester is reacted with a dialkyl hydroxymethylphosphonate **142.6**, prepared as described in Synthesis, 4, 327, 1998, in the presence of triphenyl phosphine, triethylamine and diethyl azodicarboxylate, to afford the thioether **142.7**. The tert. butyl group is removed by treatment with formic acid at ambient temperature, as described in J. Org. Chem., 42, 3972, 1977, to yield the carboxylic acid **142.8**. Using the above procedures, but employing, in place of the thiol **142.5**, different phenols or thiols **142.1** and/or different hydroxyalkyl phosphonates **142.2**, the corresponding products **142.4** are obtained.

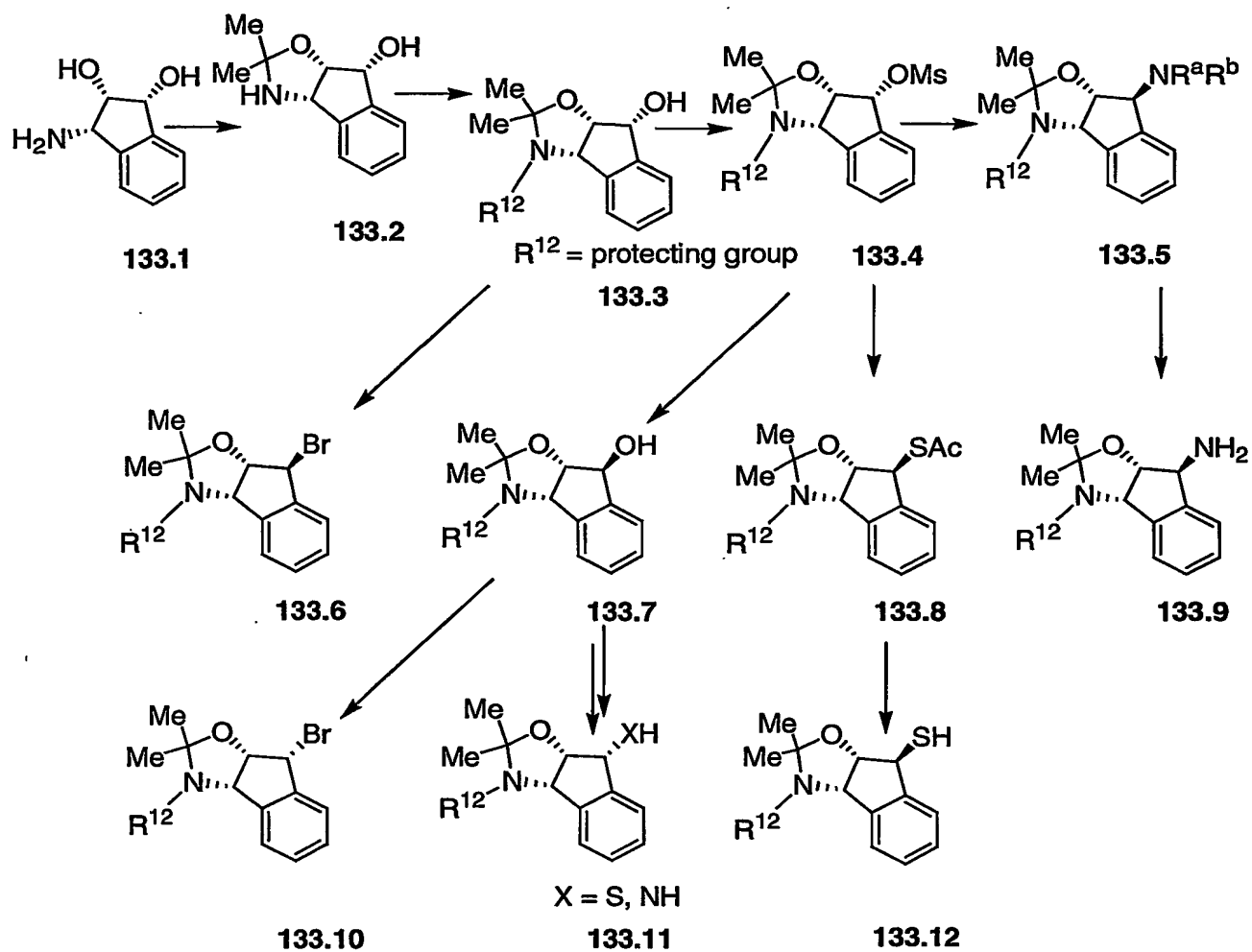
Scheme 143 depicts the preparation of phenylpropionic acids linked to a phosphonate ester by means of an aromatic or heteroaromatic ring. The products **143.3** are obtained by means of an alkylation reaction in which a bromomethyl aryl or heteroaryl phosphonate **143.1** is reacted with a carboxyl-protected hydroxy, thio or amino-substituted phenylpropionic acid **140.1**. The

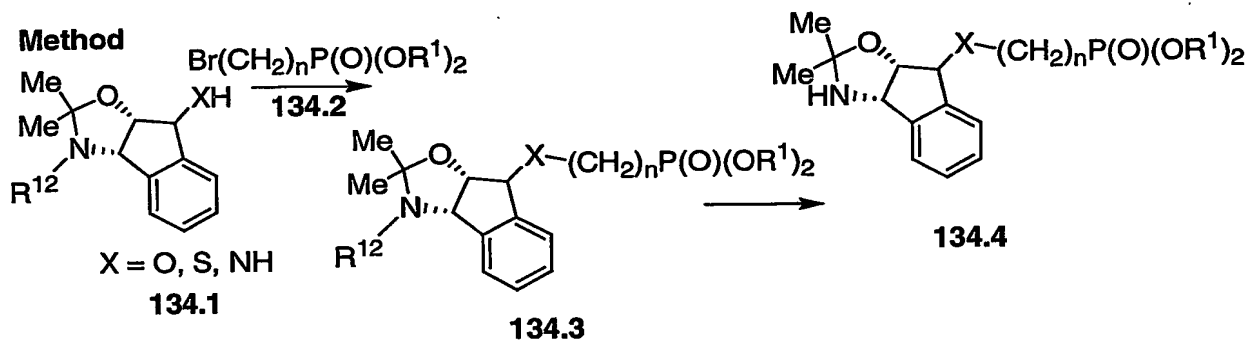
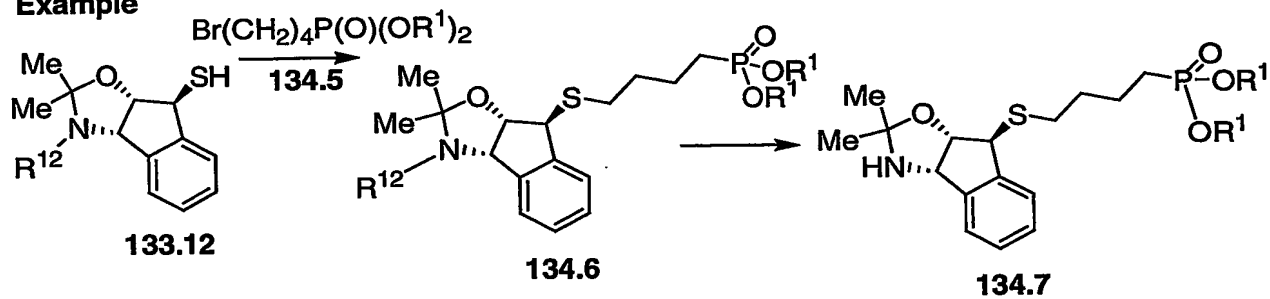
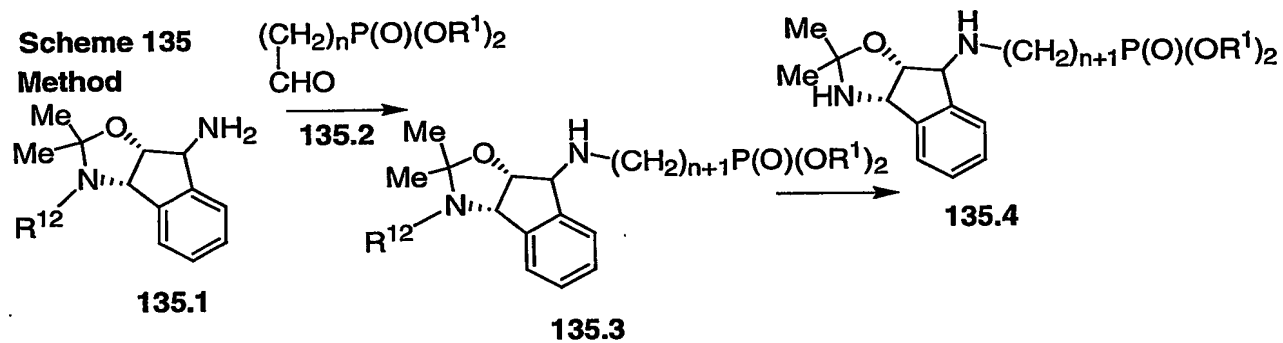
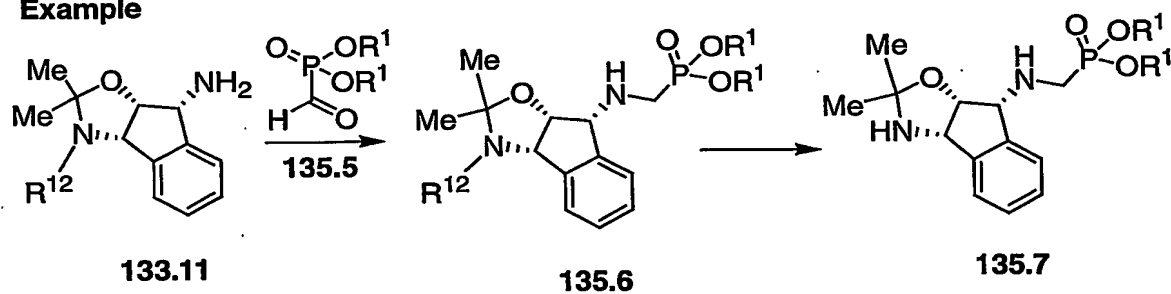
reaction is conducted in the presence of a base, the nature of which is determined by the substituent X in the reactant **140.1**. For example, if X is O, a strong base such as lithium hexamethyldisilylazide or sodium hydride is employed. If X is S or N, an organic or inorganic base, such as diisopropylethylamine or cesium carbonate is employed. The alkylated product **143.2** is then deprotected to afford the carboxylic acid **143.3**.

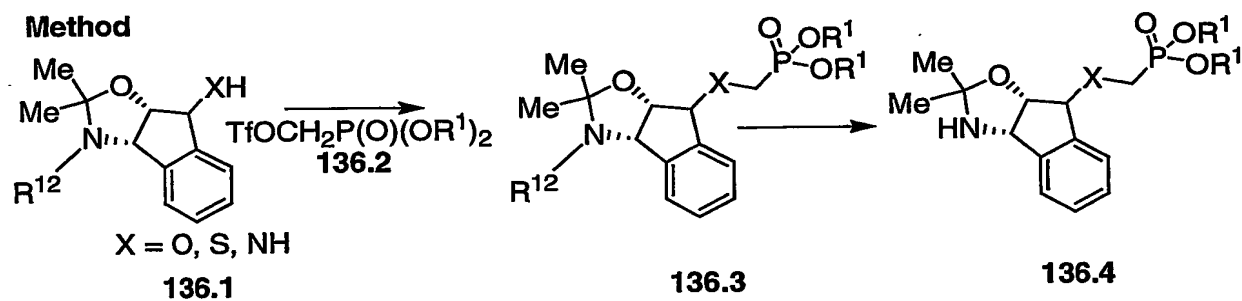
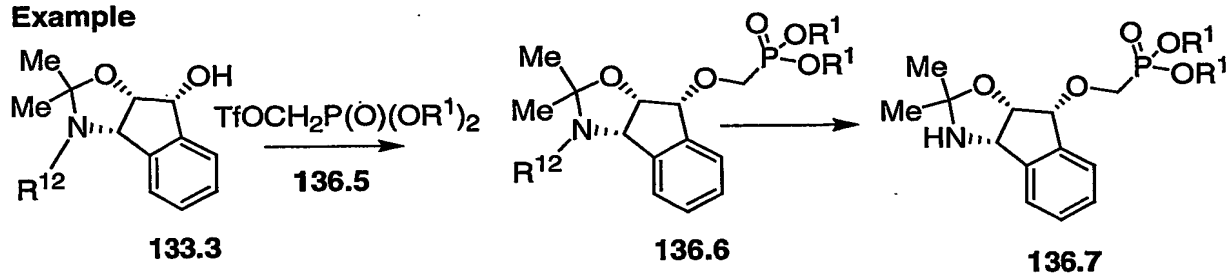
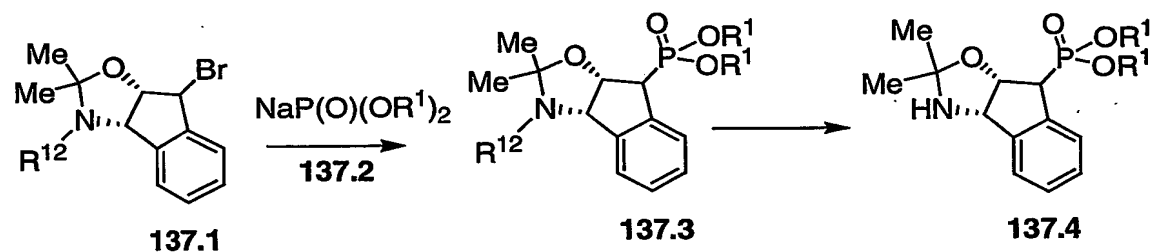
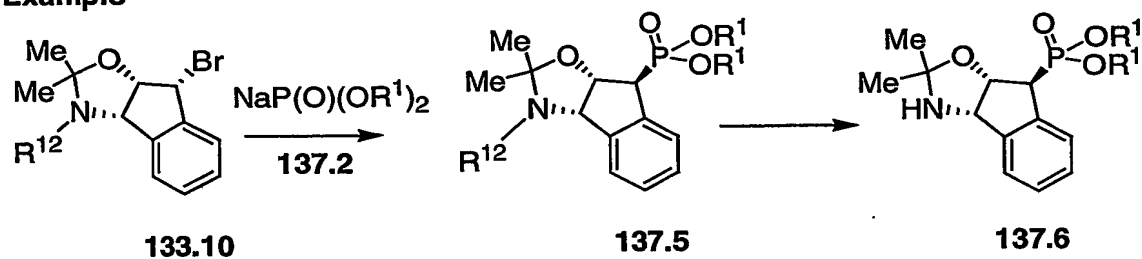
For example, 3-(4-aminophenyl)propionic acid (Aldrich) is reacted with tert. butyl chlorodimethylsilane and imidazole in dimethylformamide, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 262, to afford the silyl ester **143.4**. This compound is reacted with an equimolar amount of a dialkyl 4-bromomethylbenzylphosphonate **143.5**, prepared as described in Tet. Lett., 1998, 54, 9341, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the product **143.6**. The silyl ester is removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carboxylic acid **143.7**.

Using the above procedures, but employing, in place of the amino compound **143.4**, different phenols, mercaptans or amines **140.1**, and/or different halomethyl phosphonates **143.1**, the corresponding products **143.3** are obtained.

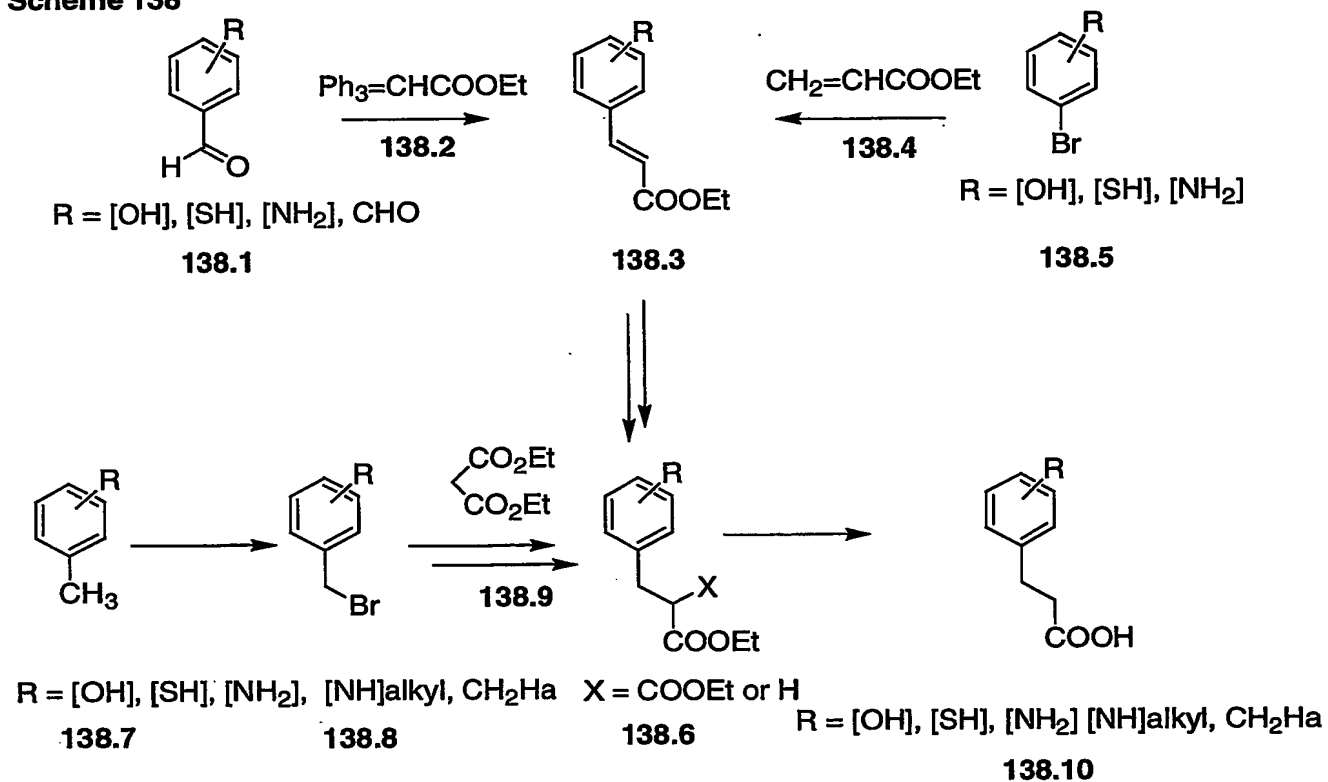
Scheme 133



Scheme 134**Method****Example****Scheme 135****Method****Example**

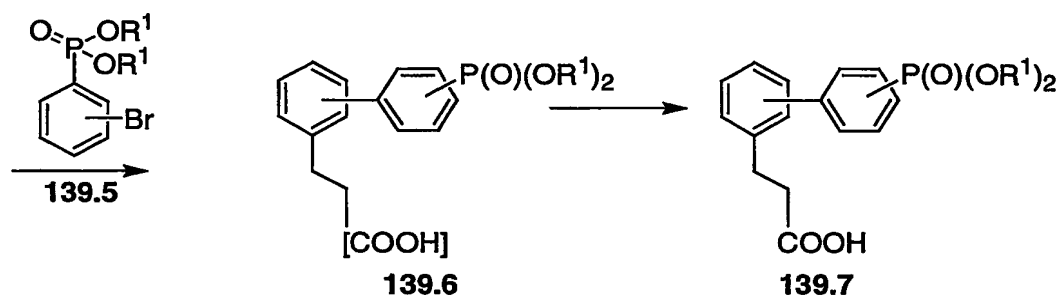
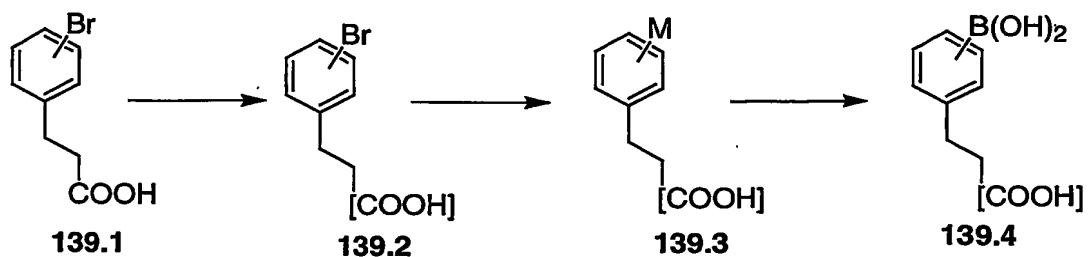
Scheme 136**Method****Example****Scheme 137****Method****Example**

Scheme 138

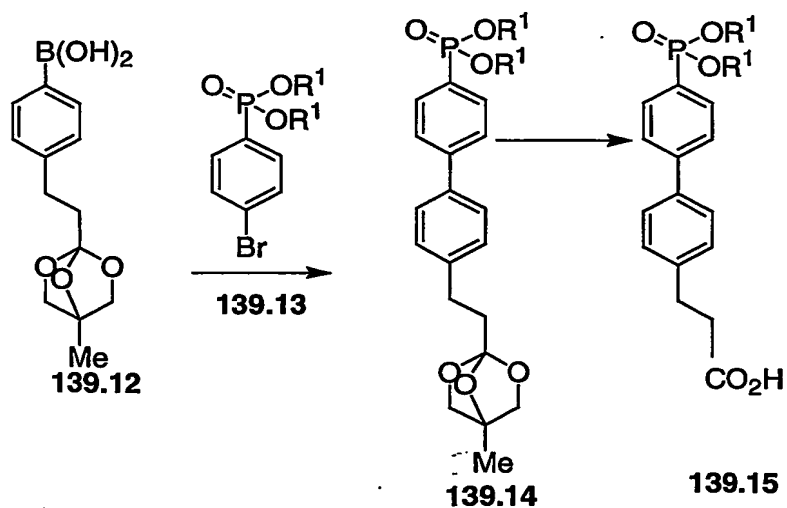
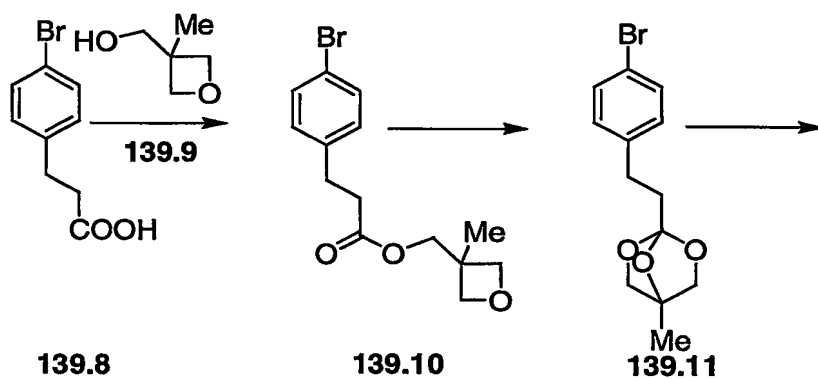


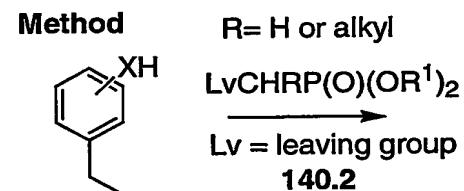
Scheme 139

Method

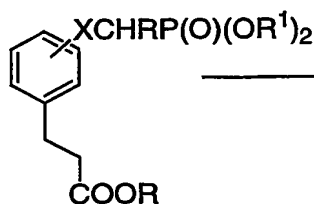
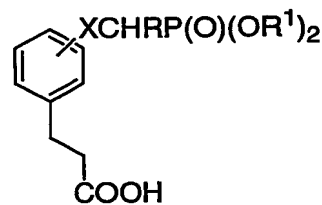
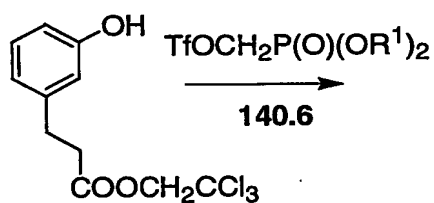
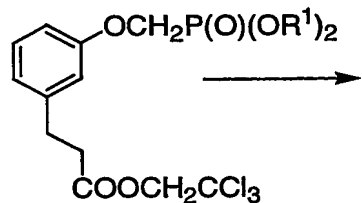
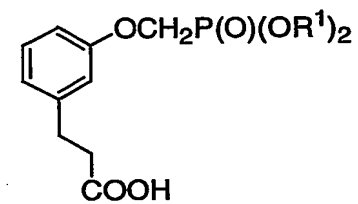
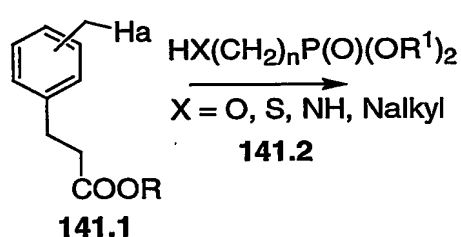
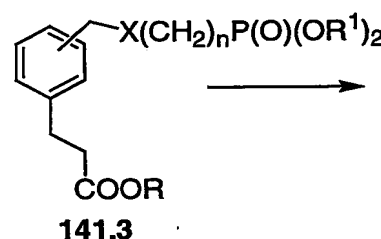
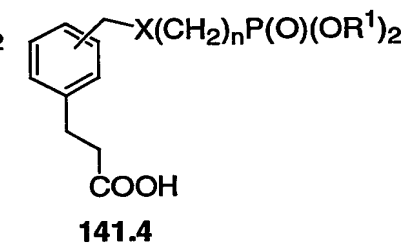
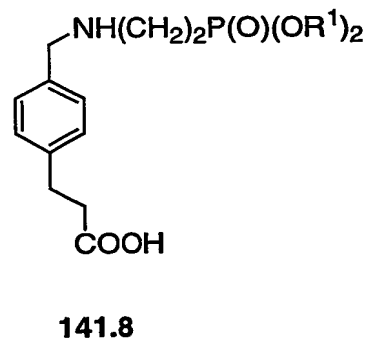
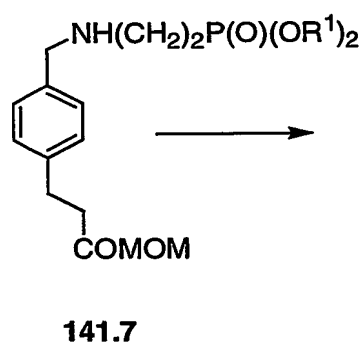
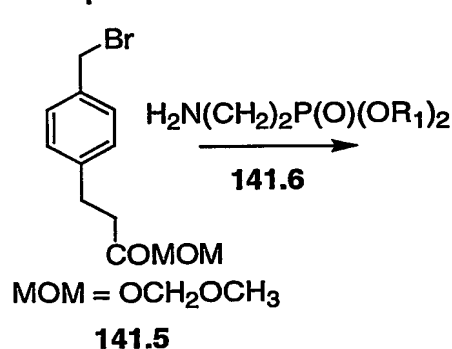


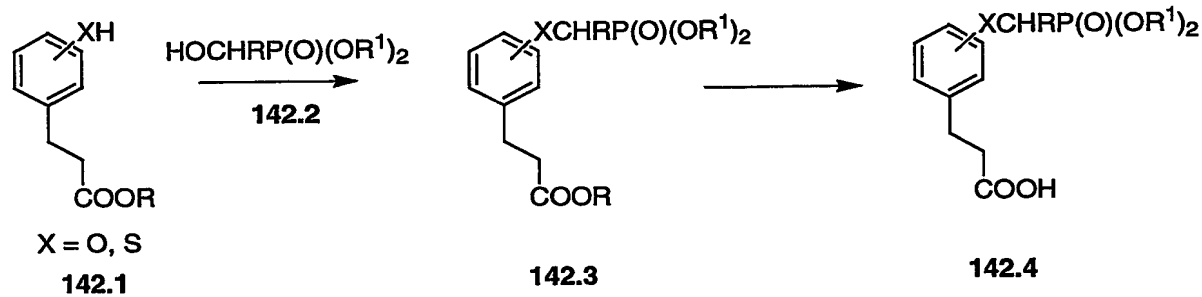
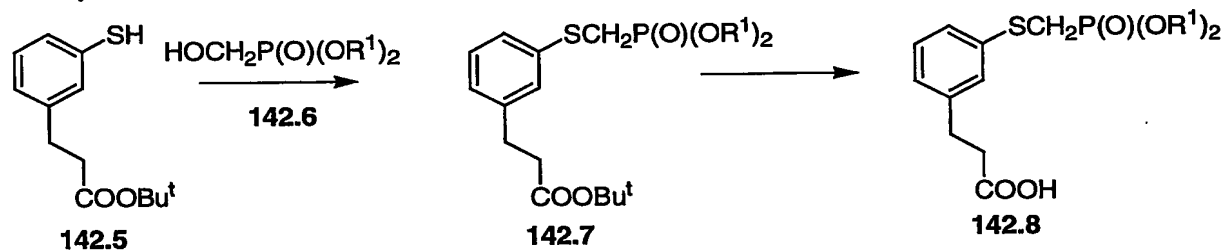
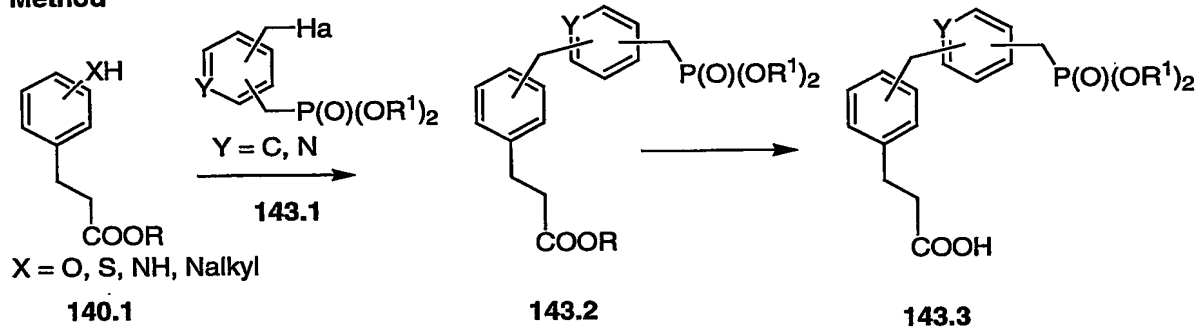
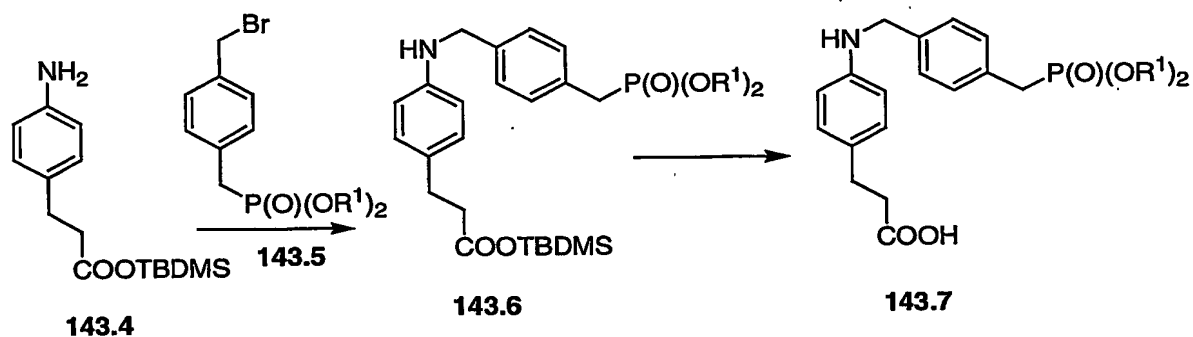
Example



Scheme 140**Method**

X = O, S, NH, Nalkyl

140.1**140.3****140.4****Example****140.5****140.7****140.8****Scheme 141****Method****141.1****141.3****141.4****Example**

Scheme 142**Method****Example****Scheme 143****Method****Example**

Preparation of the phosphonate-containing thiophenol derivatives 7.1.

Schemes 144 - 153 describe the preparation of phosphonate-containing thiophenol derivatives 7.1 which are employed in the preparation of the phosphonate ester intermediates 2, 14 and 19 in which X is sulfur, and of the intermediate 15 in which X' is sulfur.

Scheme 144 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 144.1 is protected to afford the product 144.2. The protection and deprotection of thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 144.3, to afford the phosphonate ester 144.4. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The thiol protecting group is then removed, as described above, to afford the thiol 144.5.

For example, 3-bromothiophenol 144.6 is converted into the 9-fluorenylmethyl (Fm) derivative 144.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 144.3 to afford the phosphonate ester 144.8. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The compound 144.7 is reacted, in toluene solution at reflux, with a dialkyl phosphite 144.3, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 144.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 144.9.

Using the above procedures, but employing, in place of 3-bromothiophenol **144.6**, different thiophenols **144.1**, and/or different dialkyl phosphites **144.3**, the corresponding products **144.5** are obtained.

5 Scheme **145** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **145.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkylolithium reagent, to afford the metallated derivative **145.3**. The latter compound is reacted with a halodialkyl phosphite **145.4** to afford the product **145.5**; deprotection then affords the
10 thiophenol **145.6**

For example, 4-bromothiophenol **145.7** is converted into the S-triphenylmethyl (trityl) derivative **145.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 287. The product is converted into the lithium derivative **145.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio
15 compound is reacted with a dialkyl chlorophosphite **145.10** to afford the phosphonate **145.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **145.12**.

Using the above procedures, but employing, in place of the bromo compound **145.7**, different halo compounds **145.1**, and/or different halo dialkyl phosphites **145.4**, there are obtained the
20 corresponding thiols **145.6**.

Scheme **146** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **146.1** is subjected to free-radical bromination to
25 afford a bromomethyl product **146.2**. This compound is reacted with a sodium dialkyl phosphite **146.3** or a trialkyl phosphite, to give the displacement or rearrangement product **146.4**, which upon deprotection affords the thiophenol **146.5**.

For example, 2-methylthiophenol **146.5** is protected by conversion to the benzoyl derivative **146.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **146.8**. This material is reacted with a sodium dialkyl
30 phosphite **146.3**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **146.9**.

Alternatively, the bromomethyl compound **146.8** is converted into the phosphonate **146.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **146.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. $100^\circ C$ to produce the phosphonate **146.9**. Deprotection of the phosphonate **146.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **146.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **146.8**, different bromomethyl compounds **146.2**, there are obtained the corresponding thiols **146.5**.

Scheme **147** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **147.1** is reacted with a dialkyl hydroxyalkylphosphonate **147.2** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **147.3**. Deprotection then yields the O- or S-linked products **147.4**.

For example, 3-hydroxythiophenol, **147.5**, is converted into the monotrityl ether **147.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **147.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **147.8**.

Removal of the trityl protecting group, as described above, then affords the thiophenol **147.9**. Using the above procedures, but employing, in place of the phenol **147.5**, different phenols or thiophenols **147.1**, there are obtained the corresponding thiols **147.4**.

Scheme **148** illustrates the preparation of thiophenols **148.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **148.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **148.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **148.3**. Deprotection then affords the thiol **148.4**.

For example, 4-methylaminothiophenol **148.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298, to afford the S-acetyl product **148.6**. This material is then reacted with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate **148.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **148.8**. Preferably, equimolar amounts of the phosphonate **148.7** and the amine **148.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient
5 temperatures, to afford the phosphonate product **148.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **148.9**.

Using the above procedures, but employing, in place of the thioamine **148.5**, different phenols, thiophenols or amines **148.1**, and/or different phosphonates **148.2**, there are obtained the
10 corresponding products **148.4**.

Scheme **149** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **149.2**. In this procedure, a suitably protected
15 hydroxy, thio or amino substituted thiophenol **149.1** is reacted with a dialkyl bromoalkyl phosphonate **149.2** to afford the product **149.3**. Deprotection then affords the free thiophenol **149.4**.

For example, 3-hydroxythiophenol **149.5** is converted into the S-trityl compound **149.6**, as described above. This compound is then reacted with a dialkyl 4-bromobutyl phosphonate
20 **149.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **149.8**. Deprotection, as described above, then affords the thiol **149.9**.

25 Using the above procedures, but employing, in place of the phenol **149.5**, different phenols, thiophenols or amines **149.1**, and/or different phosphonates **149.2**, there are obtained the corresponding products **149.4**.

Scheme **150** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by
30 means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **150.2** is coupled with an aromatic bromo compound **150.1**. The coupling of aryl halides with olefins

- by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
- 5 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **150.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **150.4**, or the saturated analog **150.6**.
- 10 For example, 3-bromothiophenol is converted into the S-Fm derivative **150.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **150.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
- 15 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **150.9**. Deprotection, as described above, then affords the thiol **150.10**. Optionally, the initially formed unsaturated phosphonate **150.9** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme 138, to yield the saturated product **150.11**, which upon deprotection affords the thiol **150.12**.
- 20 Using the above procedures, but employing, in place of the bromo compound **150.7**, different bromo compounds **150.1**, and/or different phosphonates **150.2**, there are obtained the corresponding products **150.4** and **150.6**

- Scheme 151 illustrates the preparation of an aryl-linked phosphonate ester **151.4** by means of
- 25 a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **151.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in *J. Org. Chem.*, 49, 5237, 1984. A coupling reaction then affords the
- 30 diaryl product **151.3** which is deprotected to yield the thiol **151.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in *Protective Groups in Organic*

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **151.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **151.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **151.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **151.8**. Using the above procedures, but employing, in place of the boronate **151.5**, different boronates **151.1**, and/or different phosphonates **151.2**, there are obtained the corresponding products **151.4**.

Scheme **152** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **152.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **152.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **152.3** is then deprotected to afford the thiol **152.4**.

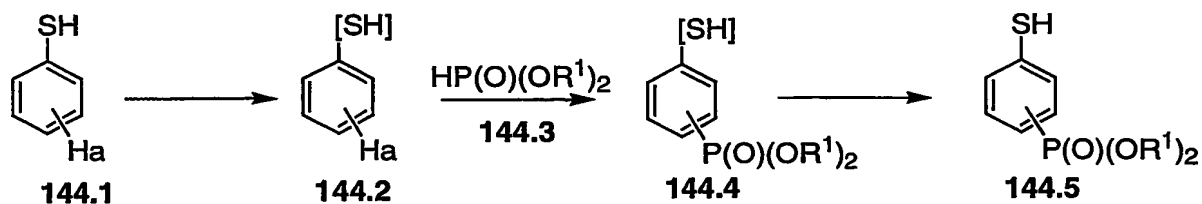
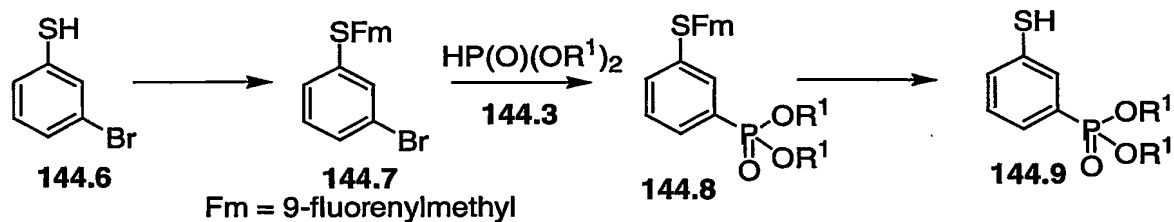
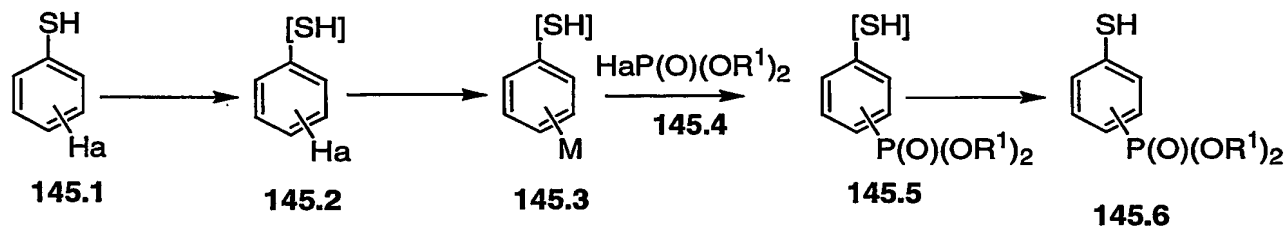
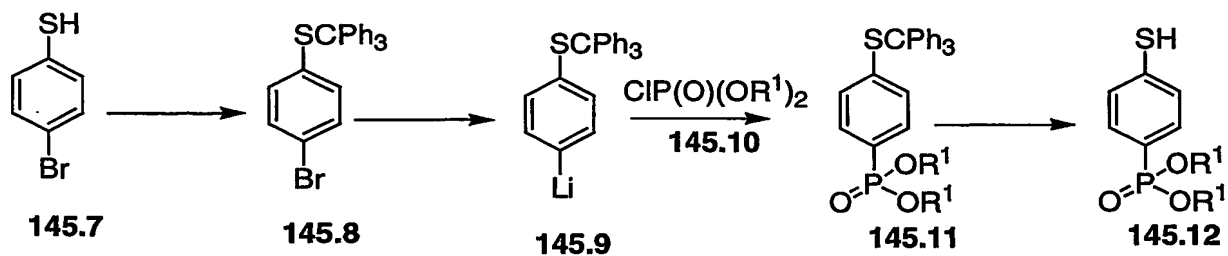
For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **152.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **152.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **152.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **152.7** thus obtained is deprotected, as described above, to afford the thiol **152.8**.

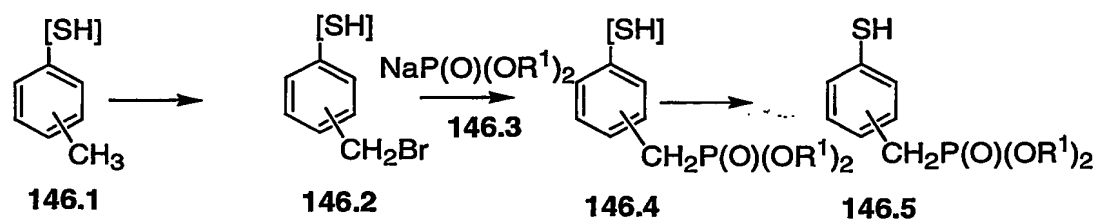
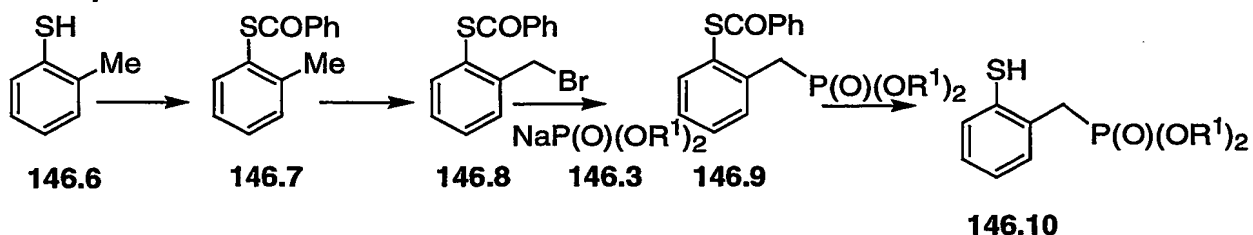
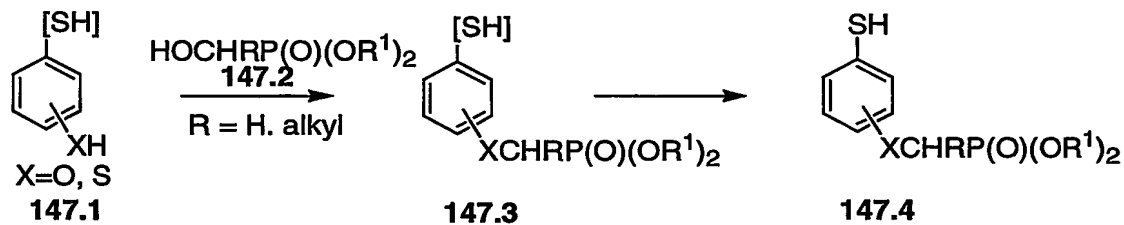
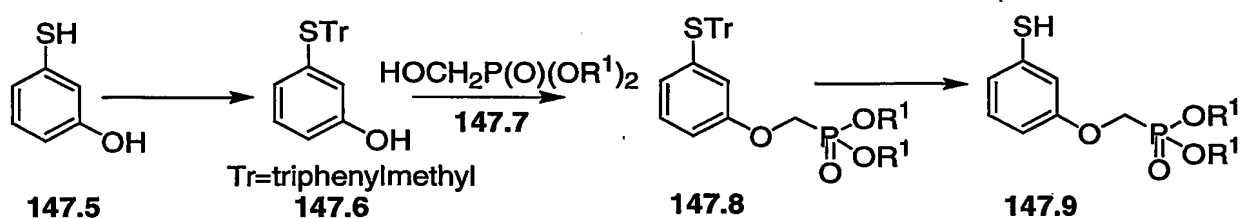
Using the above procedures, but employing, in place of the thiophenol **152.5**, different phenols, thiophenols or amines **152.1**, and/or different phosphonates **152.2**, there are obtained the corresponding products **152.4**.

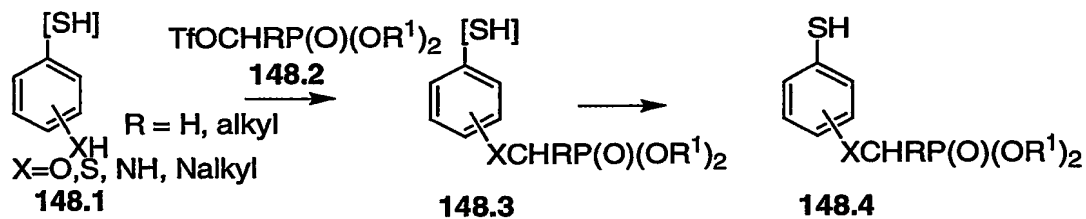
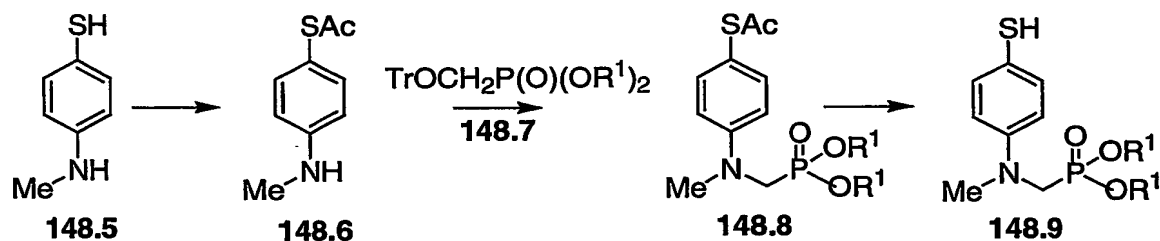
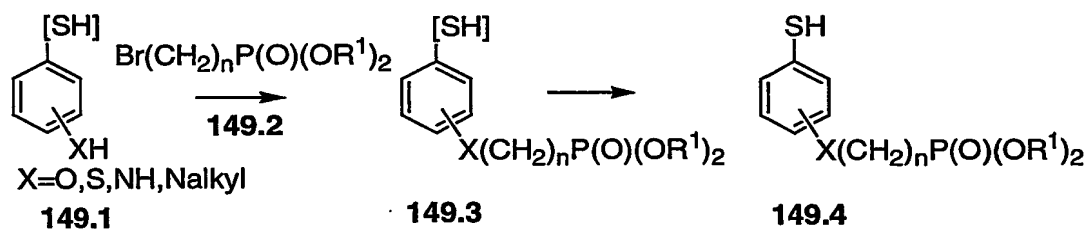
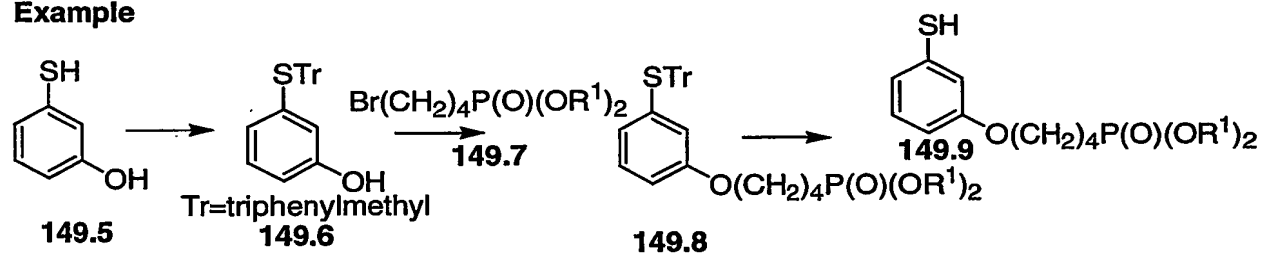
Scheme **153** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

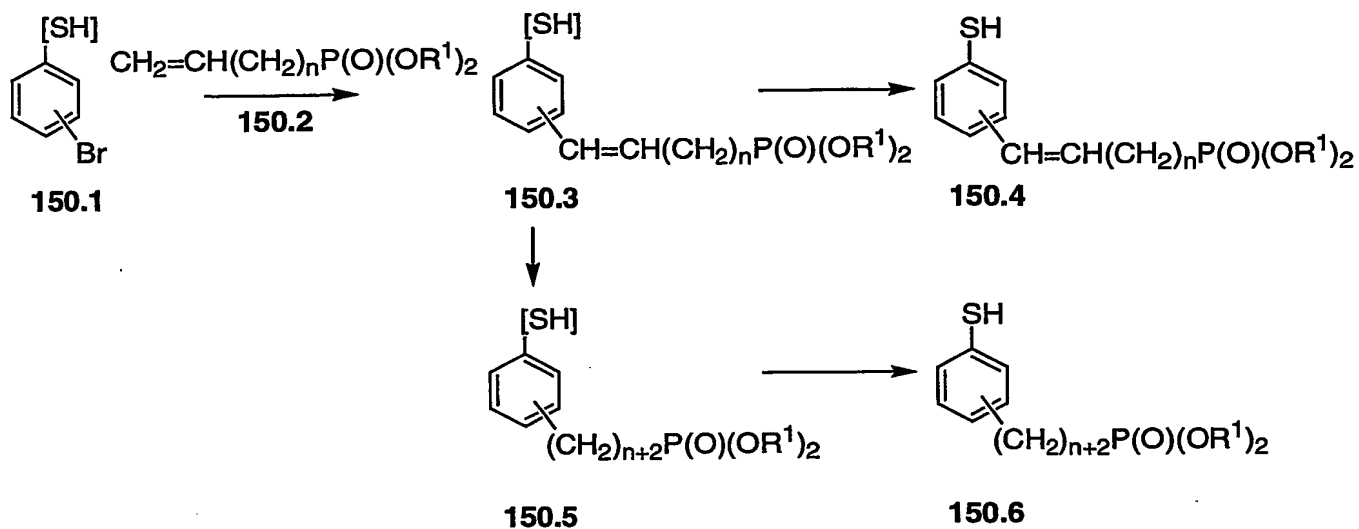
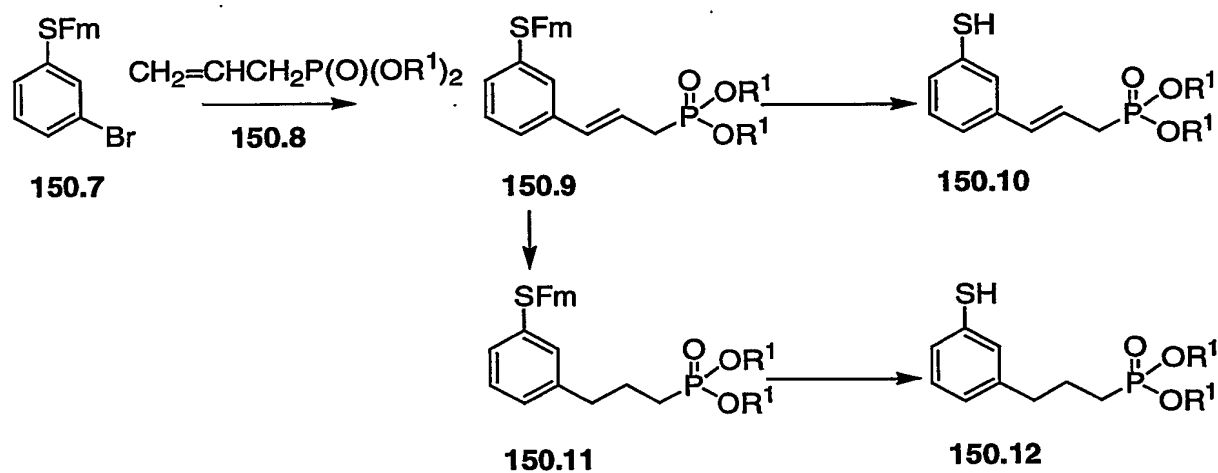
In this procedure, a suitably protected thiophenol **153.1**, for example an indoline (in which X-Y is $(\text{CH}_2)_2$), an indole (X-Y is $\text{CH}=\text{CH}$) or a tetrahydroquinoline (X-Y is $(\text{CH}_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **153.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **153.3**. Deprotection, as described above, then affords the thiol **153.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **153.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **153.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **153.7**, using the conditions described above for the preparation of the phosphonate **148.8**, (Scheme 148), to yield the phosphonate **153.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **153.9**.

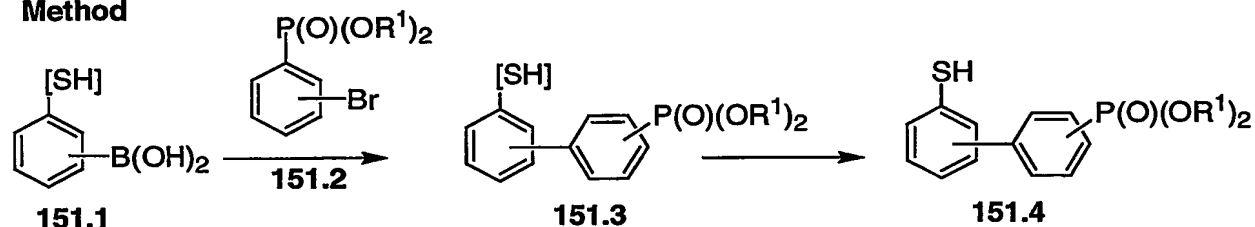
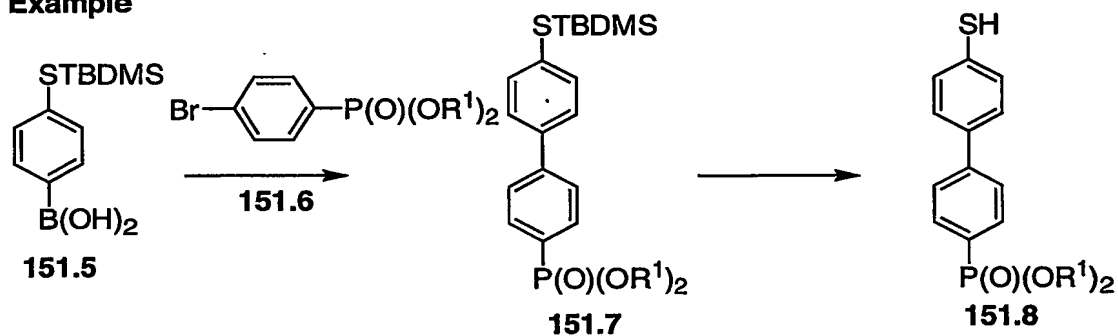
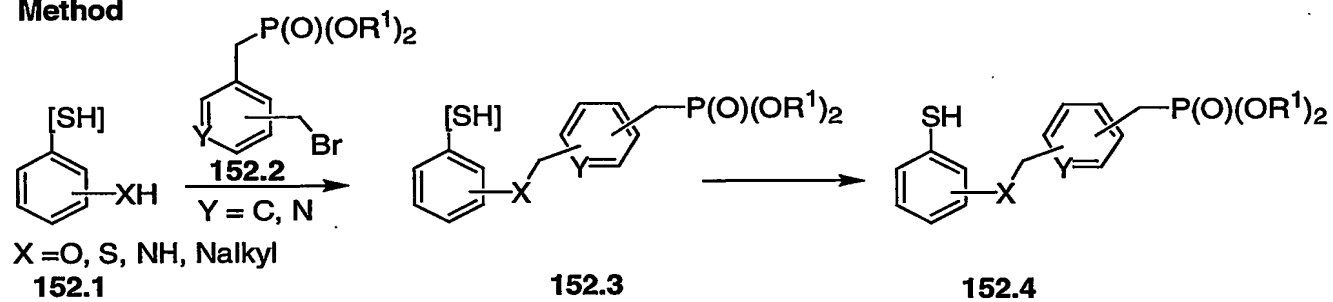
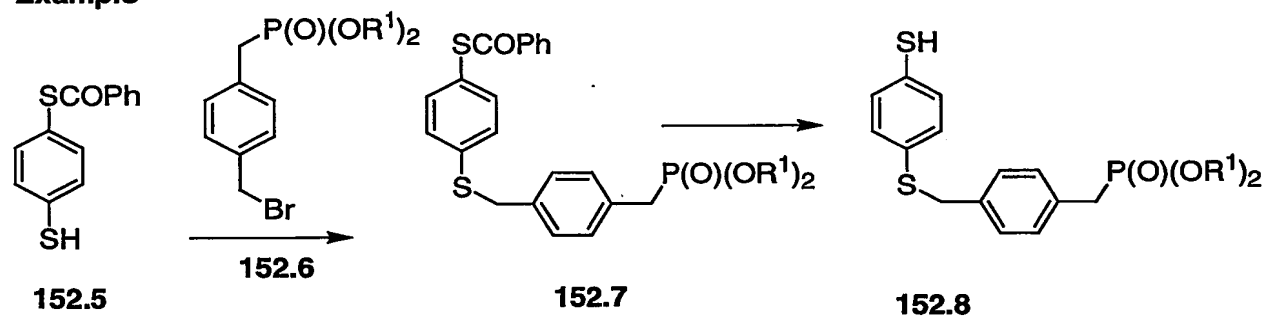
Using the above procedures, but employing, in place of the thiol **153.5**, different thiols **153.1**, and/or different triflates **153.2**, there are obtained the corresponding products **153.4**.

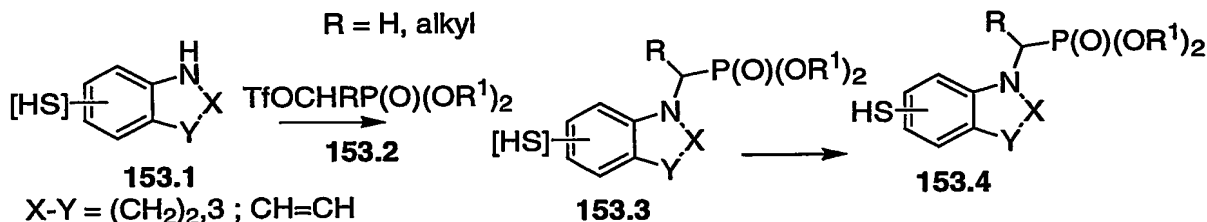
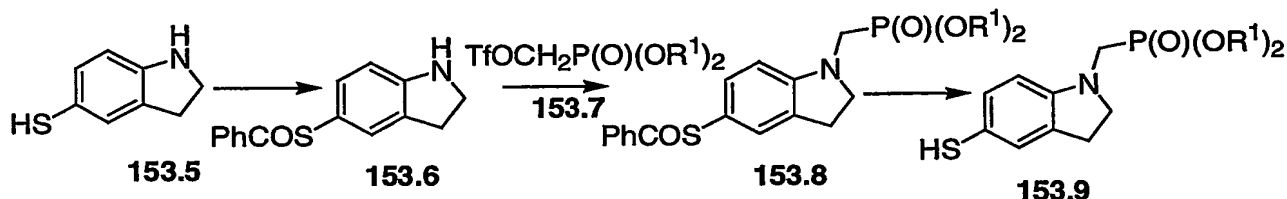
Scheme 144**Method****Example****Scheme 145****Method****Example**

Scheme 146**Method****Example****Scheme 147****Method****Example**

Scheme 148**Method****Example****Scheme 149****Method****Example**

Scheme 150**Method****Example**

Scheme 151**Method****Example****Scheme 152****Method****Example**

Scheme 153**Method****Example**

Preparation of tert-butylamine derivatives 9.3 and 25.4 incorporating phosphonate groups.

5

Schemes 154 – 158 illustrate the preparation of the tert. butylamine derivatives 9.3 and 25.4 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br, which are employed in the preparation of the intermediate phosphonate esters 3, 7, 11 and 20.

10

Scheme 154 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide 154.1 is reacted with a trialkyl phosphite 154.2, under the conditions of the Arbuzov reaction, as described in Scheme 137, to afford the phosphonate 154.3, which is then deprotected to give the amine 154.4.

15

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide 154.6, is heated with a trialkyl phosphite at ca 150°C to afford the product 154.7. Deprotection then affords the free amine 154.8. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion is effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group is removed by treatment of the substrate with triethylsilane,

20

triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group is also removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Using the above procedures, but employing different trialkyl phosphites, there are obtained the corresponding amines **154.4**.

Scheme **155** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. A protected alcohol or thiol **155.1** is reacted with a dialkyl bromoalkylphosphonate **155.2**, to afford the displacement product **155.3**. Deprotection, if needed, then yields the amine **155.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **155.5** is reacted with a dialkyl 4-bromobutyl phosphonate **155.6**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate **155.7**. Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine **155.8**.

Using the above procedures, but employing different alcohols or thiols **155.1**, and/or different bromoalkylphosphonates **155.2**, there are obtained the corresponding ether and thioether products **155.4**.

Scheme **156** describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain is unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **156.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **156.2**, to afford the acetylenic phosphonate **156.3**. The coupled product **156.3** is deprotected to afford the amine **156.4**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **156.5** and **156.6** respectively.

For example, 2-amino-2-methylprop-1-yne **156.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **156.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide

in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **156.2** to afford the phosphonate **156.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **156.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents
5 for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **156.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **156.12**.
10 Using the above procedures, but employing different acetylenic amines **156.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **156.4**, **156.5** and **156.6**.

Scheme **157** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

15 In this method, an aminopropyl-substituted cyclic amine **157.1** is reacted with a limited amount of a bromoalkyl phosphonate **157.2**, using, for example, the conditions described above (Scheme **149**) to afford the displacement product **157.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate **157.5**, prepared as described in Synthesis, 1994, 9, 909, to
20 afford the displacement product **157.6**.

Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, different cyclic amines **157.1**, and/or different bromoalkylphosphonates **157.2**, there are obtained the corresponding products **157.3**.

25 Scheme **158** illustrates the preparation of the amides **9.3** which are employed in the preparation of the phosphonate esters **3**. In this procedure, the carboxylic acids **158.1**, the structures of which are illustrated in Chart **10**, compounds **C1 - C16**, are converted into the BOC-protected derivatives **155.8**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and
30 P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine is reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like. The carboxylic acid

158.2 is then coupled, as described in Scheme 1, with the tert. butylamine derivatives 25.4, or precursors thereto, the preparation of which is described in Schemes 154 - 157, to afford the amide 158.3. The BOC group is then removed to yield the amine 9.3. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of pyridine intermediates 13.1 incorporating phosphonate substituents.

Schemes 159 - 163, described the preparation of chloromethyl or formyl pyridine derivatives incorporating phosphonate moieties. Scheme 164 illustrates the conversion of the above compounds into the piperazine derivatives 13.1 which are employed in the preparation of the phosphonate esters 4.

Scheme 159 illustrates the preparation of chloromethyl-substituted pyridines in which a phosphonate moiety is directly attached to the pyridine ring.

In this procedure, a halo-substituted methylpyridine 159.1 is reacted with a dialkyl phosphite 159.2, to afford the phosphonate product 159.3. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in J. Med. Chem., 35, 1371, 1992. The product 159.3 is then converted into the chloromethyl derivative 159.4 by means of a chlorination reaction. The chlorination of benzylic methyl groups is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. A variety of free-radical chlorinating agents are employed.

For example, 3-bromo-5-methylpyridine, 159.5 (ChemPacific) is reacted with an equimolar amount of a dialkyl sodium phosphite, 13.2 in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate 159.6. The latter compound is then chlorinated, for example by the use of one molar equivalent of phenyliodonium dichloride, as described in J. Org. Chem., 29, 3692, 1964, to prepare the chloromethyl compound 159.7.

Using the above procedures, but employing, in place of the bromomethyl pyridine 159.5, different halomethyl pyridines 159.1, and/or different dialkyl phosphites 159.2 the corresponding products 159.4 are obtained.

Scheme 160 depicts the preparation of chloromethyl pyridines incorporating a phosphonate group attached to the pyridine ring by means of a carbon link. In this procedure, a bis(chloromethyl)pyridine 160.1 is reacted with a sodium dialkyl phosphite 146.3, employing, for example, procedures described in J. Med. Chem., 35, 1371, 1992, to afford the displacement product 160.2.

For example, 3,5-bis(chloromethyl)pyridine 160.3, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, is reacted with one molar equivalent of a dialkyl sodium phosphite 146.3 in tetrahydrofuran, at ambient temperature, to afford the product 160.4.

Using the above procedures, but employing, in place of the bis(chloromethyl) compound 160.3, different bis(chloromethyl) pyridines 160.1, and/or different dialkyl sodium phosphites 146.3 the corresponding products 160.2 are obtained.

Scheme 161 illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine nucleus by means of a saturated or unsaturated carbon chain. In this procedure, a suitably protected halo-substituted pyridine carboxaldehyde 161.1 is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme 150, with a dialkyl alkenyl phosphonate 161.2. Methods for the protection of aldehydes are described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 175. The protected aldehyde 161.1 is reacted with an olefinic phosphonate 161.2, in the presence of a palladium (0) catalyst, to afford the coupled product 161.3. Deprotection of the aldehyde group then affords the product 161.6. Alternatively, the unsaturated compound 161.3 is reduced to afford the saturated analog 161.5, which upon deprotection yields the saturated analog 161.7. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, 5-bromopyridine-3-carboxaldehyde 161.8 (ChemPacific) is converted into the dimethyl acetal, by reaction with methanolic ammonium chloride, as described in J. Org. Chem., 26, 1156, 1961. The acetal 161.9 is then reacted with a dialkyl butenyl phosphonate 161.10, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in J. Med. Chem., 1992, 35, 1371, to afford the coupled product 161.11. Deprotection, for example by treatment with formic acid in pentane, as described in Synthesis, 651, 1983, yields the free aldehyde 161.13.

The product is reduced, for example by reaction with diimide, as described in J. Org. Chem., 30, 3965, 1965, to afford the saturated product **161.12**.

Using the above procedures, but employing, in place of the aldehyde **161.8**, different aldehydes **161.1**, and/or different phosphonates **161.2**, the corresponding products **161.6** and **161.7** are obtained.

Scheme **162** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine by a heteroatom and a carbon chain. In this procedure, a 2- or 4-halo-substituted pyridine aldehyde **162.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **162.2**. The preparation of alkoxypyridines by the reaction of alkoxides with halopyridines is described, for example, in J. Am. Chem. Soc., 82, 4414, 1960. The preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in Chemistry of Heterocyclic Compounds, Pyridine and its derivatives, E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **162.3**.

For example, a tetrahydrofuran solution of 2-bromo-pyridine-5-aldehyde **162.4**, prepared as described in Tet. Lett., 2001, 42, 4841, is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **162.5**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **162.6**.

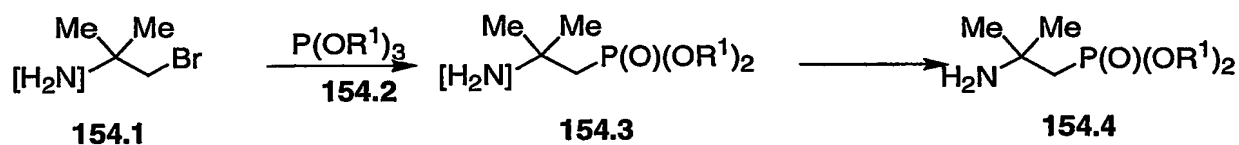
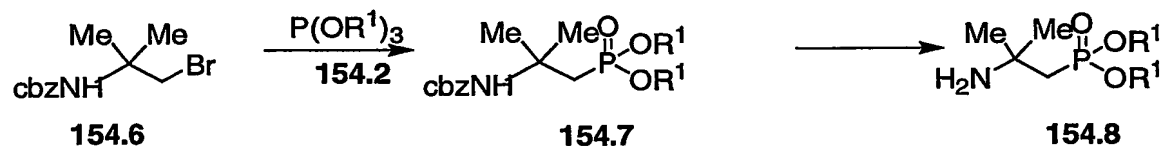
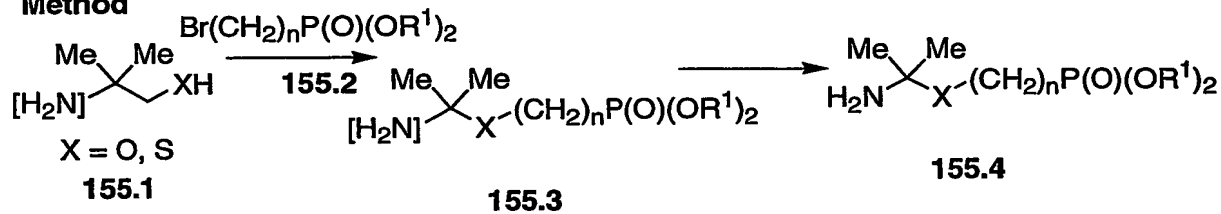
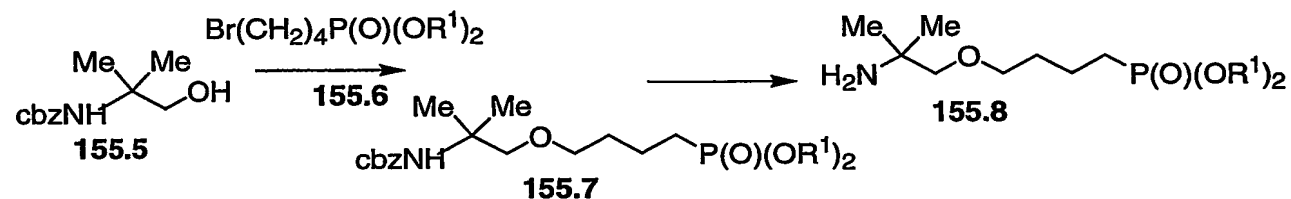
Using the above procedures, but employing, in place of the haloaldehyde **162.4**, different haloaldehydes **162.1**, and/or different hydroxy or thio-alkyl phosphonates **162.2**, the corresponding products **162.3** are obtained.

Scheme **163** depicts the preparation of pyridine aldehydes **163.3** in which the phosphonate group is attached to the pyridine nucleus by means of a chain incorporating a nitrogen atom. In this procedure, a pyridine dicarboxaldehyde **163.1** is reacted with a dialkyl aminoalkyl phosphonate **163.2**, in the presence of a reducing agent, so as to effect a reductive amination reaction, yielding the product **163.3**. The preparation of amines by means of reductive amination of aldehydes is described, for example, in Advanced Organic Chemistry, F. A.

Carey, R. J. Sundberg, Plenum, 2001, part B, p. 269. The reactants are combined in an inert solvent such as an alcohol or ether, and treated with a reducing agent such as, for example, sodium cyanoborohydride or sodium triacetoxy borohydride, so as to yield the amine product **163.3**.

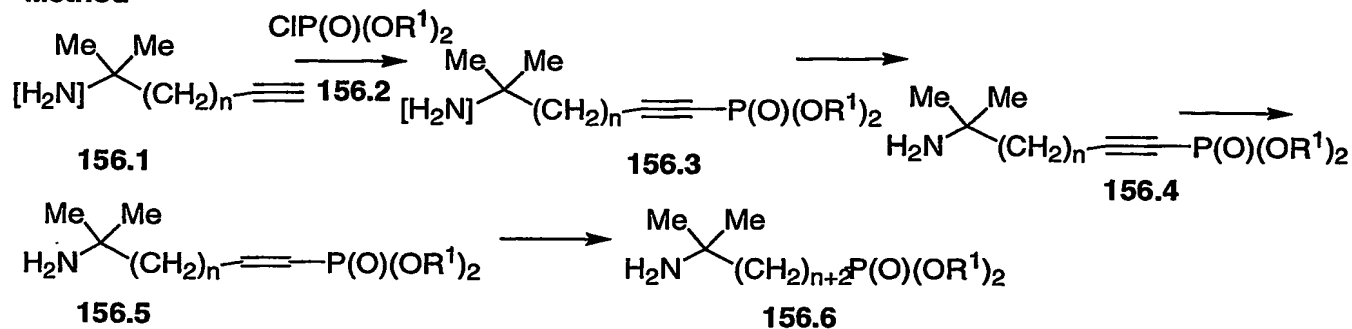
- 5 For example, equimolar amounts of pyridine 3,5-dicarboxaldehyde **163.4**, prepared as described in Tet. Lett., 1994, 35, 6191, and a dialkyl 2-aminoethyl phosphonate **163.5** prepared as described in J. Org. Chem., 2000, 65, 676, are reacted with sodium cyanoborohydride in isopropanol containing acetic acid, at ambient temperature, so as to produce the amine product **163.6**
- 10 Using the above procedures, but employing, in place of the dicarboxaldehyde **163.4**, different dicarboxaldehydes **163.1**, and/or different aminoalkyl phosphonates **163.2**, the corresponding products **163.3** are obtained.

- Scheme **164** illustrates the incorporation of the formyl or chloromethyl pyridines, the syntheses of which are described above, into the piperazine reagent **13.1**. Compounds **164.2** in which Z is chloromethyl are reacted with the mono-protected piperazine derivatives **164.1**, the preparation of which are described in WO 9711698, to afford the alkylated product **164.3**. The preparation of amines by means of alkylation reactions is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 397. Equimolar amounts of the reactants **164.1** and the halomethyl pyridine compound **164.2**, are combined in a organic solvent such as an alcohol or dimethylformamide, in the presence of a base such as triethylamine or potassium carbonate, to give the alkylated products **164.3**. The alkylation of a piperazine derivative by a 3-chloromethylpyridine is described in WO9628439. Alternatively, the amine **164.1** is reacted with the aldehyde **164.2** to afford the product **164.3** in a reductive alkylation reaction. The preparation of amines by means of reductive amination procedures is described in Scheme **163**. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reductive alkylation reaction between 3-pyridinecarboxaldehyde and a substituted piperazine is described in WO9628439. Deprotection of the product **164.3** then yields the free amine **13.1**.

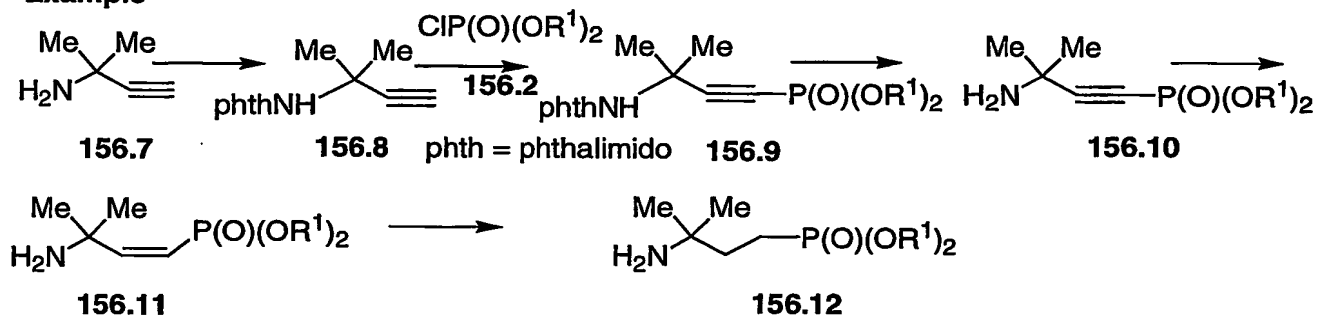
Scheme 154**Method****Example****Scheme 155****Method****Example**

Scheme156

Method

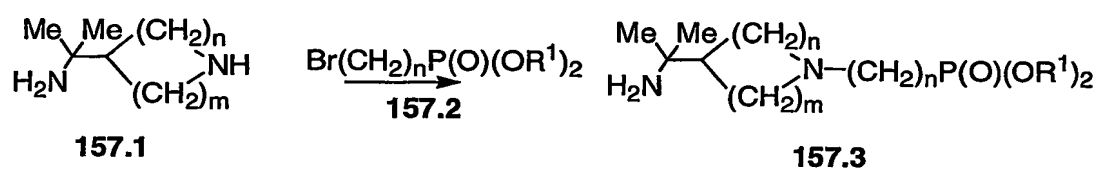


Example

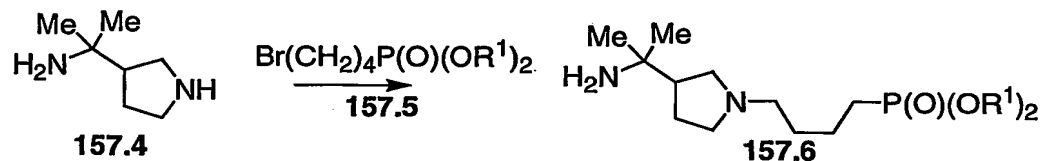


Scheme 157

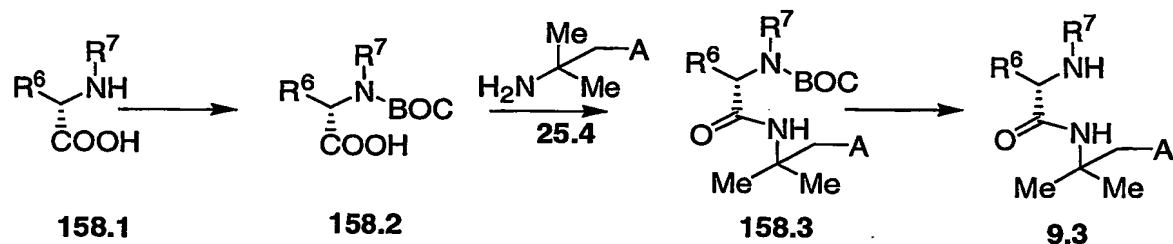
Method

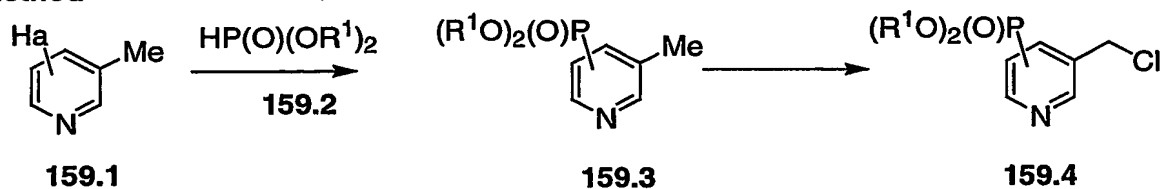
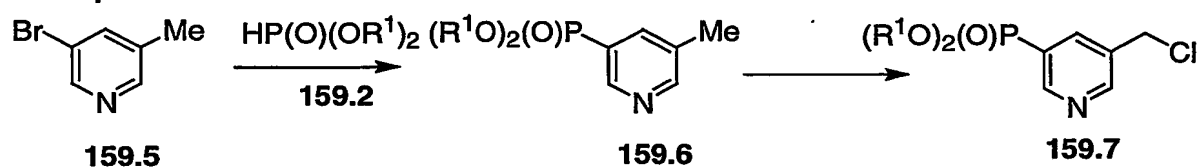
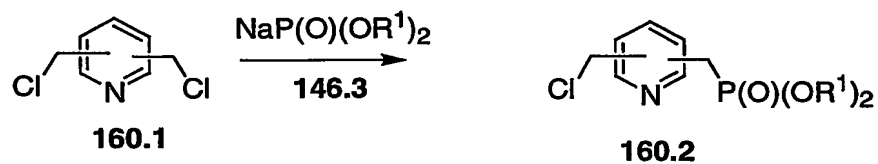
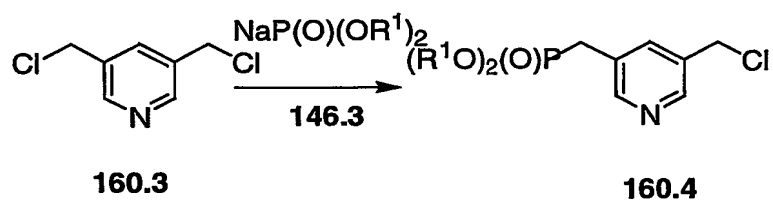


Example

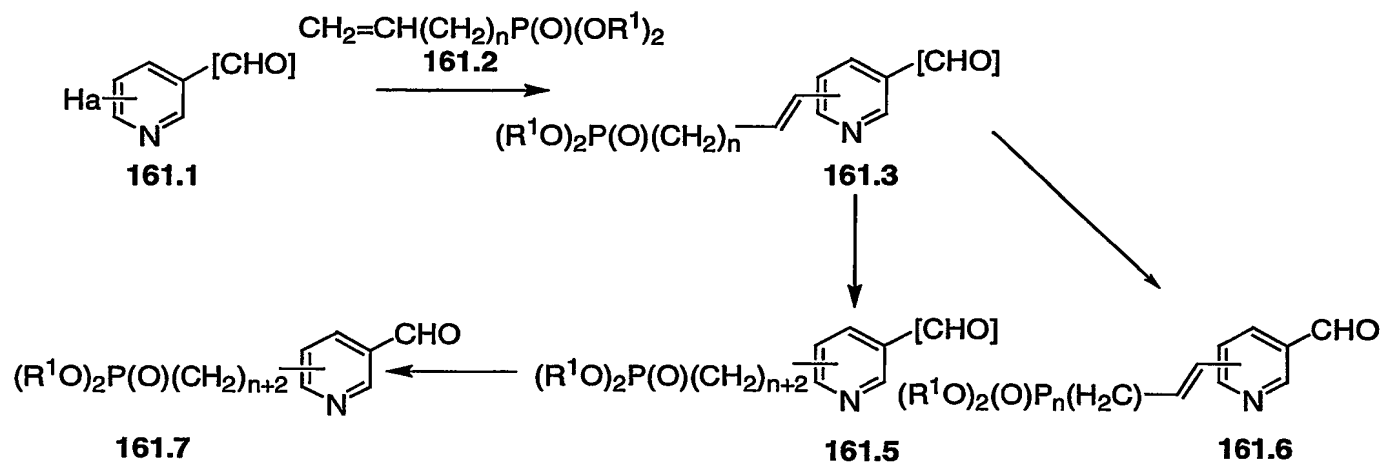


Scheme 158

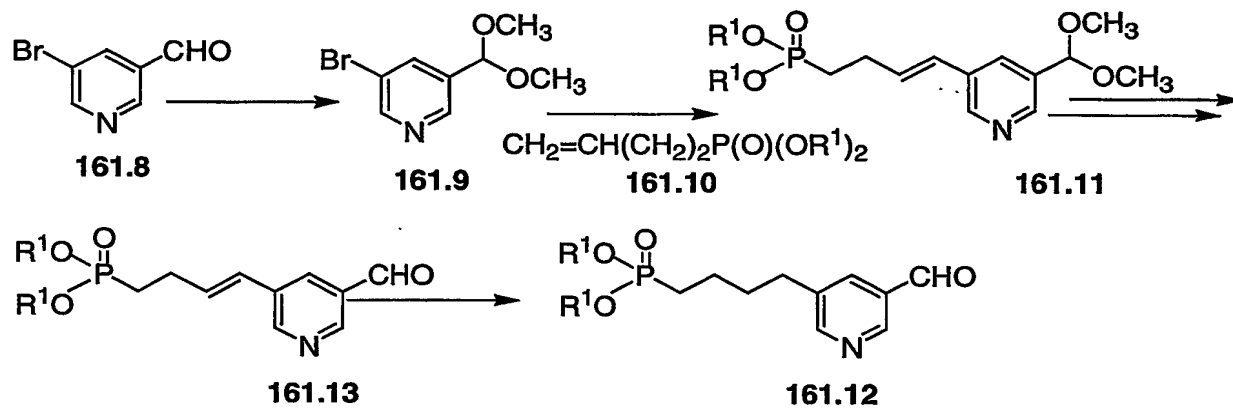


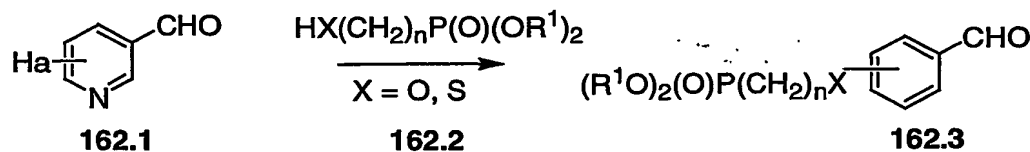
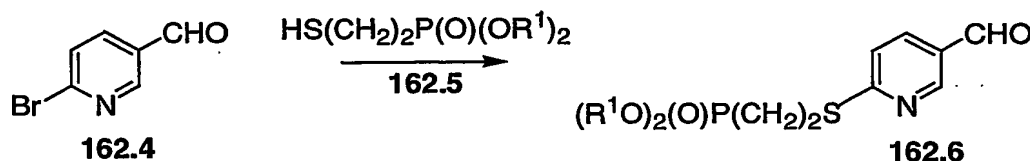
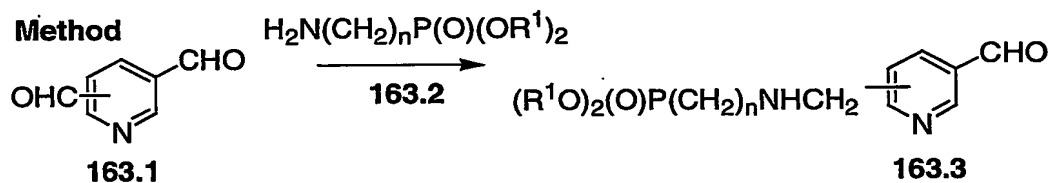
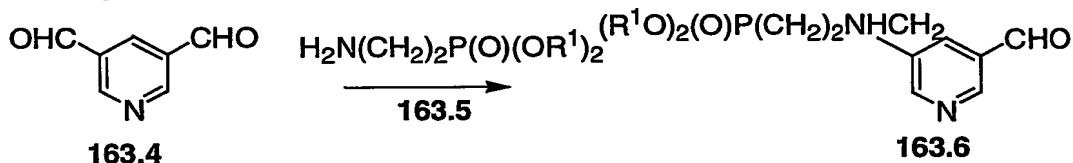
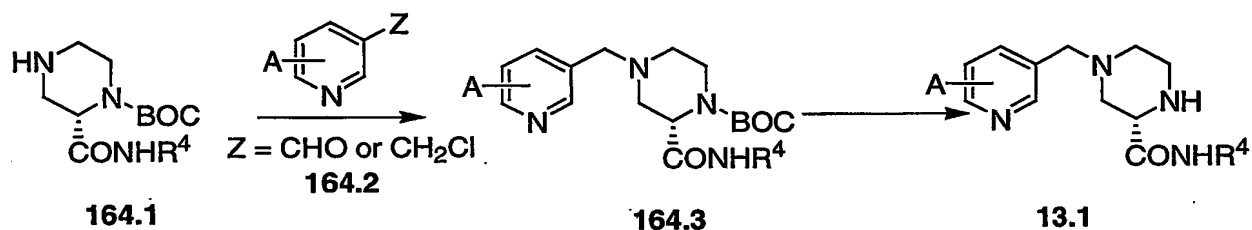
Scheme 159**Method****Example****Scheme 160****Method****Example**

Scheme 161
Method



Example



Scheme 162**Method****Example****Scheme 163****Method****Example****Scheme 164****Preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups.**

- 5 Schemes 165 - 169 illustrate the preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups, which are employed in the synthesis of the phosphonate esters 6 and 13.

Scheme 165 depicts the preparation of dimethoxybenzyl alcohols in which the phosphonate group is attached either directly to the phenyl ring or by a saturated or unsaturated alkylene

chain. In this procedure, a bromo-substituted dimethoxy benzyl alcohol is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **165.2**, to afford the coupled product **165.3**. The reaction is conducted under the conditions described in Scheme **150**. The product **165.3** is then reduced, for example by treatment with diimide, as described in Scheme **150**, to yield the saturated analog **165.4**. Alternatively, the bromo compound **165.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **144**, with a dialkyl phosphite **165.5**, to afford the phosphonate **165.6**.

For example, 4-bromo-3,5-dimethoxybenzyl alcohol **165.7**, the preparation of which is described in J. Med. Chem., 1977, 20, 299, is coupled with a dialkyl allyl phosphonate **165.8** (Aldrich) in the presence of bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **165.9**. The product is reduced, for example by treatment with diimide, as described in J. Org. Chem., 52, 4665, 1987, to yield the saturated compound **165.10**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.7**, different benzyl alcohols **165.1**, and/or different alkenyl phosphonates **165.2**, the corresponding products **165.3** and **165.4** are obtained.

As a further example, 3-bromo-4,5-dimethoxybenzyl alcohol **165.11**, the preparation of which is described in J. Org. Chem., 1978, 43, 1580, is coupled, in toluene solution at reflux, with a dialkyl phosphite **165.5**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate **165.12**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.11**, different benzyl alcohols **165.1**, and/or different dialkyl phosphites **165.5**, the corresponding products **165.6** are obtained.

Scheme **166** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted dimethoxybenzyl alcohol **166.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **166.2** to prepare the amide **166.3**.

For example, 2,6-dimethoxy-4-(hydroxymethyl)benzoic acid **166.4**, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2118, is coupled in dimethylformamide solution, in

the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide **166.6**. Using the above procedures, but employing, in place of the dimethoxybenzoic acid **166.4**, different benzoic acids **166.1**, and/or different aminoalkyl phosphites **166.2**, the corresponding products **166.3** are obtained.

Scheme **167** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an aminoalkyl or an amide group. In this procedure, an amino-substituted dimethoxybenzyl alcohol **167.1** is reacted, under reductive amination conditions, as described in Scheme **163**, with a dialkyl formylalkylphosphonate **167.2** to yield the aminoalkyl product **167.3**. Alternatively, the amino-substituted dimethoxybenzyl alcohol **167.1** is coupled, as described in Scheme **1**, with a dialkyl carboxyalkyl phosphonate **167.4**, to produce the amide **167.5**.

For example, 3-amino-4,5-dimethoxybenzyl alcohol **167.6**, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is reacted, in the presence of sodium triacetoxyborohydride, with a dialkyl formylmethyl phosphonate **167.7**, as described in Scheme **135**, to afford the aminoethyl phosphonate **167.8**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different formylalkyl phosphites **167.2**, the corresponding products **167.3** are obtained.

As a further example, 4-amino-3,5-dimethoxybenzyl alcohol **167.9**, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl phosphonoacetic acid **167.10**, (Aldrich) to afford the amide **167.11**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different carboxyalkyl phosphonates **167.4**, the corresponding products **167.5** are obtained.

Scheme **168** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an alkoxy group. In this procedure, a dimethoxyhydroxy benzyl alcohol **168.1** is reacted with a dialkyl alkylphosphonate **168.2** with a terminal leaving group to afford the alkoxy product **168.3**. The alkylation reaction is

effected in a polar organic solvent such as dimethylformamide in the presence of a base such as dimethylaminopyridine or cesium carbonate.

For example, 4-hydroxy-3,5-dimethoxybenzyl alcohol **168.4**, the preparation of which is described in J. Med. Chem. 1999, 43, 3657, is reacted in dimethylformamide at 80°C with an equimolar amount of a dialkyl bromopropyl phosphonate **168.5**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and cesium carbonate, to give the alkylated product **168.6**. Using the above procedures, but employing, in place of the phenol **168.4**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

As a further example, 4,5-dimethoxy-3-hydroxybenzyl alcohol **168.7**, prepared as described in J. Org. Chem., 1989, 54, 4105, is reacted, as described above, with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **168.8**, prepared as described in Tet. Lett., 1986, 27, 1477, to produce the alkylated product **168.9**.

Using the above procedures, but employing, in place of the phenol **168.7**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

Scheme **169** illustrates the conversion of the benzyl alcohols **169.1**, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor, prepared as described above, into the corresponding halides **169.2**. The conversion of alcohols into chlorides, bromides and iodides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff, p. 356ff and p. 358ff. For example, benzyl alcohols are transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols are transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. Benzyl alcohols are transformed into iodides by reaction with sodium iodide and boron trifluoride etherate, as described in Tet. Lett., 28, 4969, 1987, or by reaction with diphosphorus tetraiodide, as described in Tet. Lett., 1801, 1979. Benzylic chlorides or bromides are transformed into the corresponding iodides by reaction with sodium iodide in acetone or methanol, for example as described in EP 708085.

Preparation of dimethoxythiophenols 23.1 incorporating phosphonate groups.

Schemes 170 - 173 illustrate the preparation of the dimethoxythiophenols 23.1 incorporating phosphonate groups, which are used in the synthesis of the phosphonate esters 6 and 13.

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Scheme 170 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of an amide group. In this procedure, a dimethoxyamino-substituted benzoic acid 170.1 is converted into the corresponding thiol 170.2. The conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol 170.2. The product is then coupled, as described above, with a dialkyl aminoalkyl phosphonate 170.3, to yield the amide 170.4.

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For example, 5-amino-2,3-dimethoxybenzoic acid 170.5, the preparation of which is described in JP 02028185, is converted, as described above, into 2,3-dimethoxy-5-mercaptobenzoic acid 170.6. The product is then coupled, as described in Scheme 1, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 170.7, (Acros) to afford the amide 170.8.

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Using the above procedures, but employing, in place of the amine 170.5, different amines 170.1, and/or different aminoalkyl phosphonates 170.3, the corresponding products 170.4 are obtained.

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Scheme 171 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromodimethoxyaniline 171.1 is converted, as described in Scheme 170, into the corresponding thiophenol 171.2. The thiol group is then protected to give the derivative 171.3. The protection and deprotection of thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or

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adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product **171.3** is then coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl alkenyl phosphonate **171.4**, to give the alkenyl product **171.5**. Deprotection then yields the thiol **171.6**. Reduction of the double bond, for example by reaction with diimide, as described in J. Org. Chem., 52, 4665, 1987, affords the saturated product **171.7**.

For example, 4-bromo-3,5-dimethoxyaniline **171.8**, prepared as described in WO9936393, is converted, by diazotization, into 4-bromo-3,5-dimethoxythiophenol **171.9**. The product is then transformed into the S-benzoyl derivative **171.10**, by reaction with benzoyl chloride in pyridine, and the product is coupled, as described in Scheme **165**, with a dialkyl butenyl phosphonate **171.11**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, to yield the phosphonate **171.12**. Deprotection, for example by treatment with aqueous ammonia at ambient temperature, as described in J. Am. Chem. Soc., 85, 1337, 1963, then afford the thiol **171.13**. The double bond is reduced with diimide to give the saturated analog **171.14**.

Using the above procedures, but employing, in place of the amine **171.8**, different amines **171.1**, and/or different alkenyl phosphonates **171.4**, the corresponding products **171.6** and **171.7** are obtained.

Scheme **172** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group directly attached to the phenyl ring. In this procedure, a protected bromodimethoxythiophenol **172.1**, prepared, for example, from the corresponding aniline, as described above, is coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl phosphite **172.2**. The product is then deprotected to afford the phosphonate ester **172.4**.

For example, 3-bromo-4,5-dimethoxyaniline **172.5**, prepared as described in DE 2355394, is converted, as described above in Schemes **165** and **171**, into S-benzoyl 3-bromo-4,5-dimethoxythiophenol **172.6**. This compound is then coupled, in toluene solution at reflux, with a dialkyl phosphite **172.2**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate **172.7**. Deprotection, as described in Scheme **171**, then affords the thiol **172.8**.

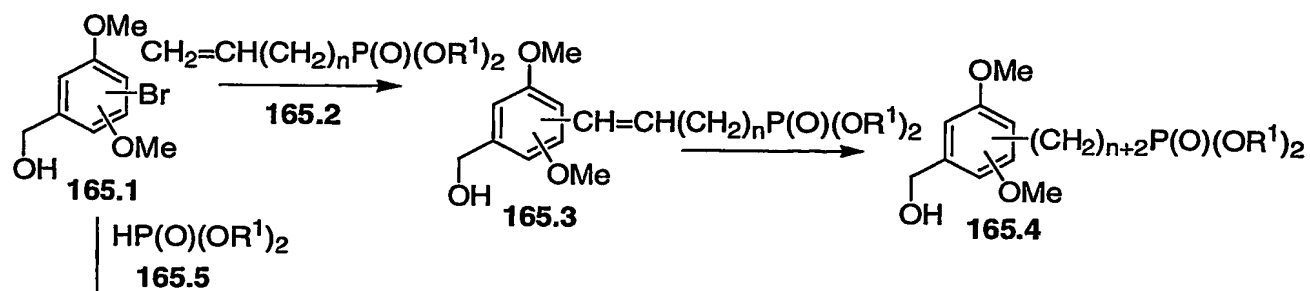
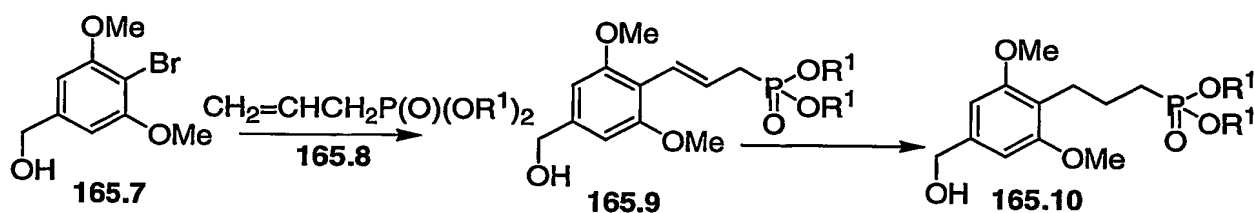
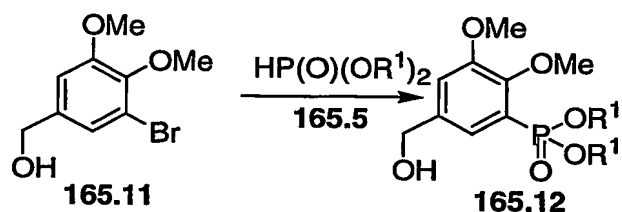
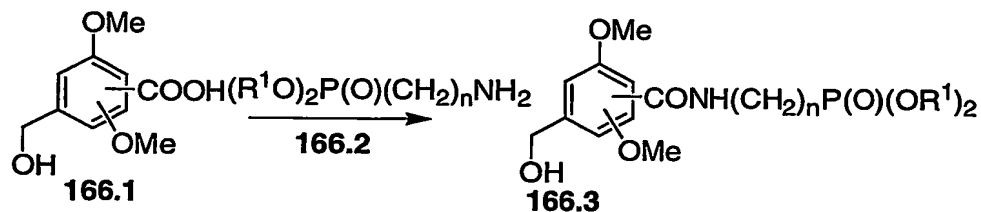
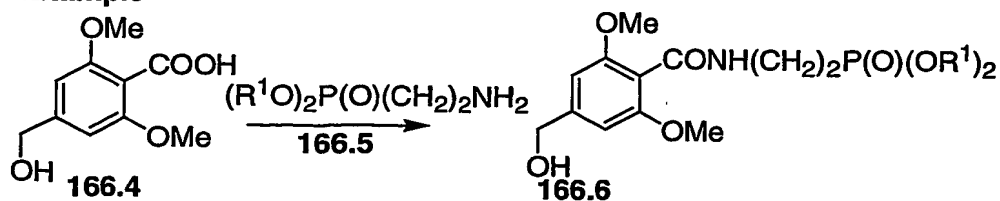
Using the above procedures, but employing, in place of the protected thiol **172.6**, different thiol **172.1**, the corresponding products **172.4** are obtained.

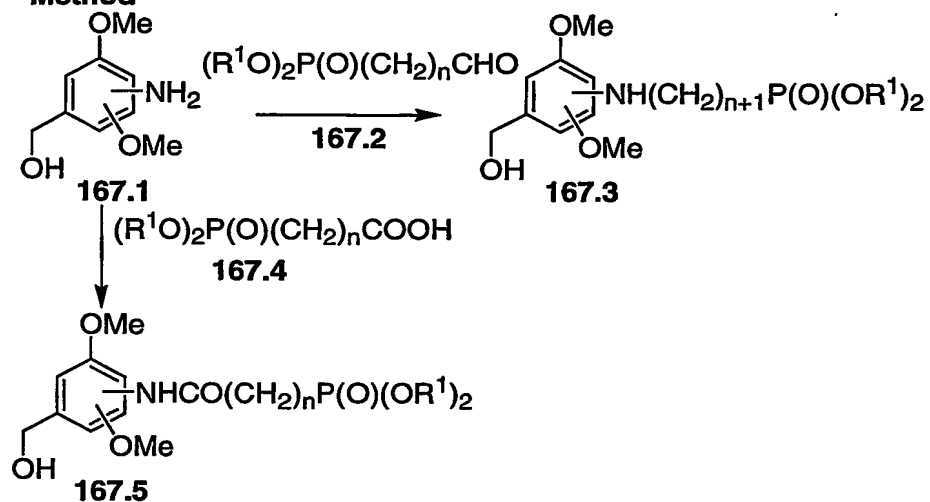
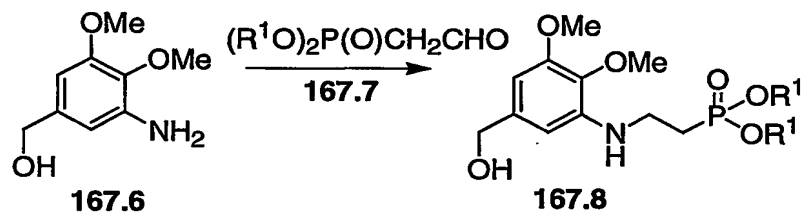
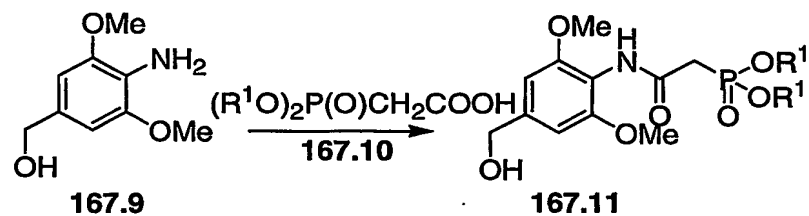
Scheme **173** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached to the phenyl ring by means of an alkoxy group. In this procedure, a dimethoxy aminophenol **173.1** is converted, via the diazo compound, into the corresponding thiophenol **173.2**. The thiol group is then protected, and the product **173.3** is alkylated, as described in Scheme **168**, with a dialkyl bromoalkyl phosphonate **173.4**. Deprotection of the product **173.5** then affords the thiophenol **173.6**.

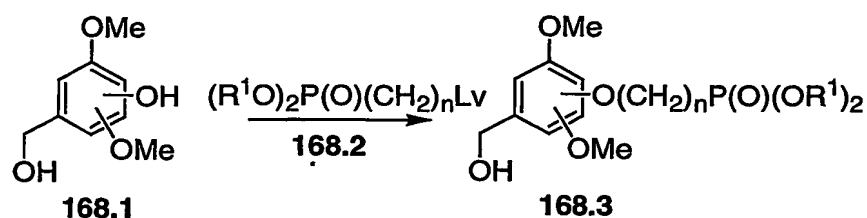
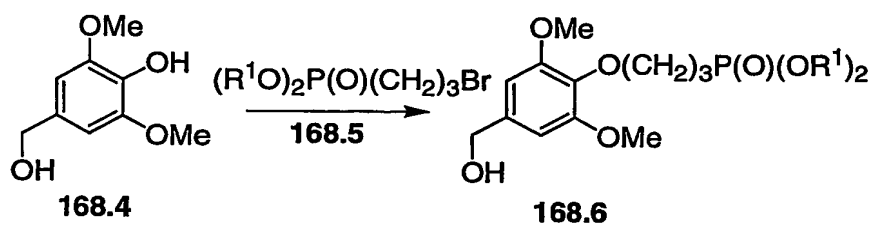
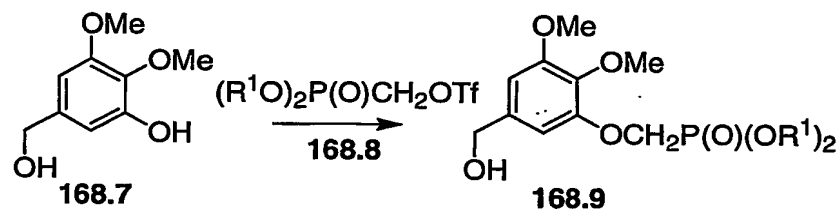
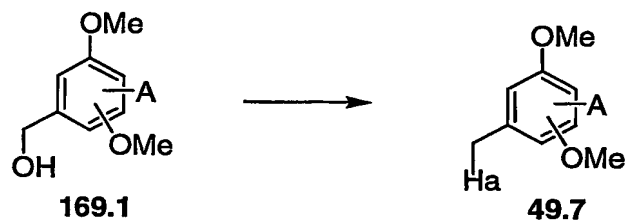
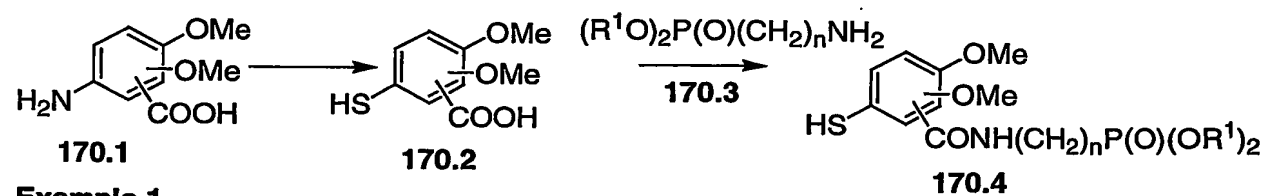
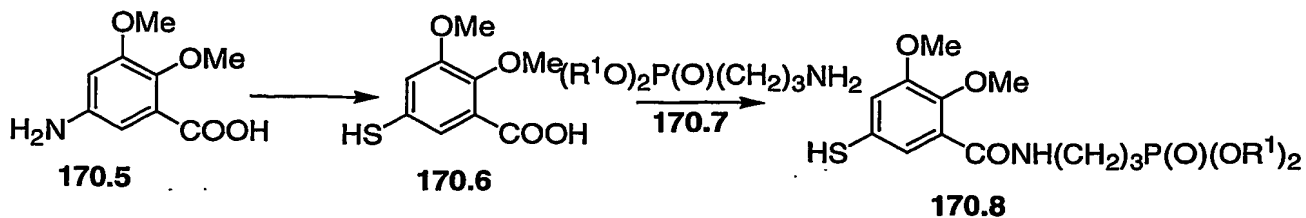
For example, 5-amino-2,3-dimethoxyphenol **173.7**, prepared as described in WO 9841512, is converted by diazotization, as described above, into the thiophenol **173.8**, and the product is protected by reaction with one molar equivalent of benzoyl chloride in pyridine, to yield the S-benzoyl product **173.9**. The latter compound is then reacted, in dimethylformamide solution at 80°C, with a dialkyl bromoethyl phosphonate **173.10** (Aldrich) and cesium carbonate, to produce the ethoxyphosphonate **173.11**. Deprotection, as described in Scheme **171**, then yields the thiol **173.12**.

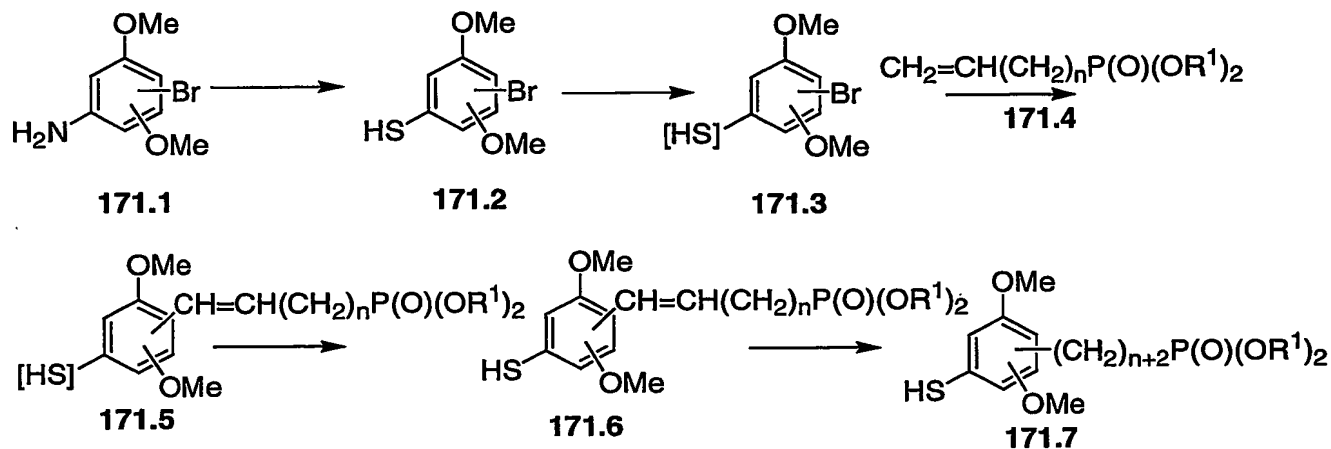
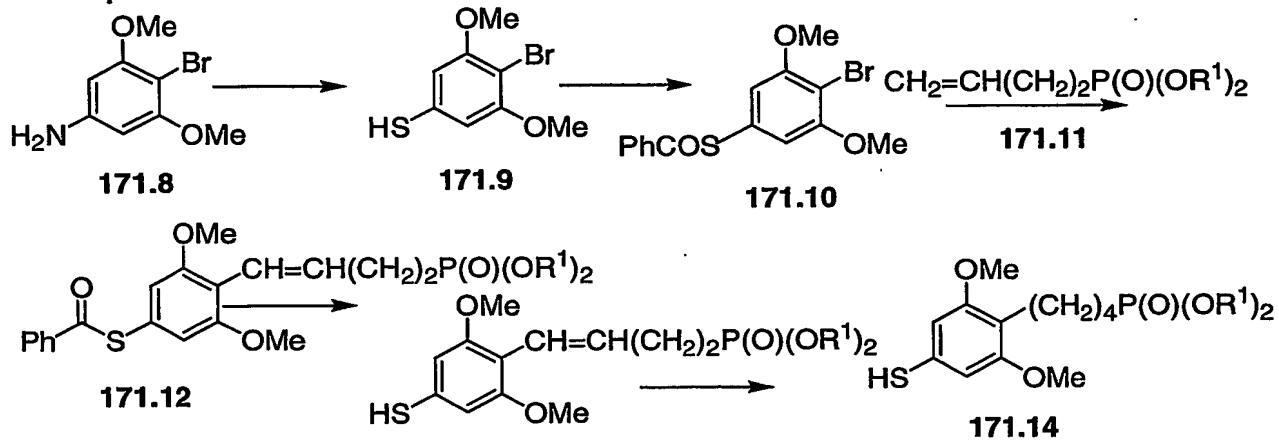
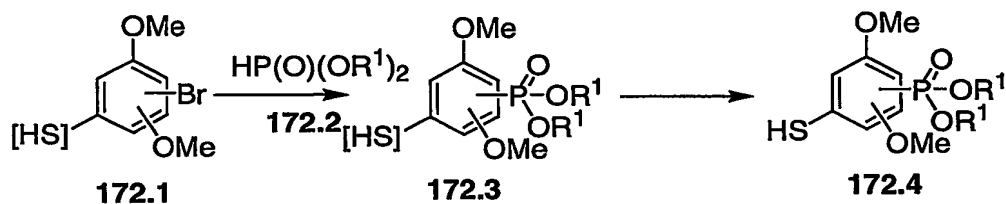
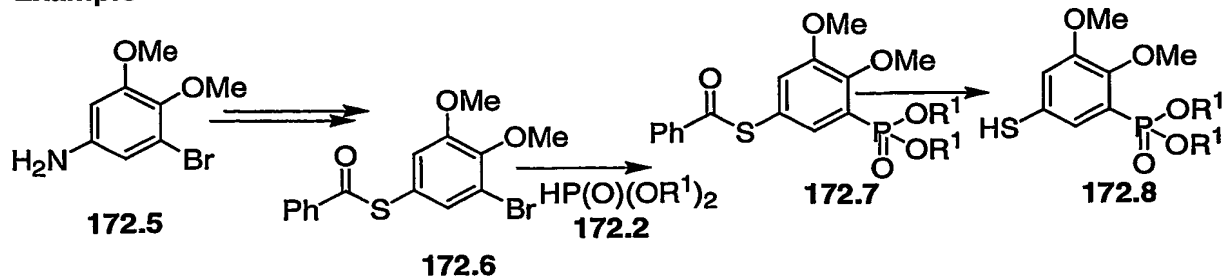
Using the above procedures, but employing, in place of the thiol **173.8**, different thiol **173.2**, and/or different bromoalkyl phosphonates **173.4**, the corresponding products **173.6** are obtained.

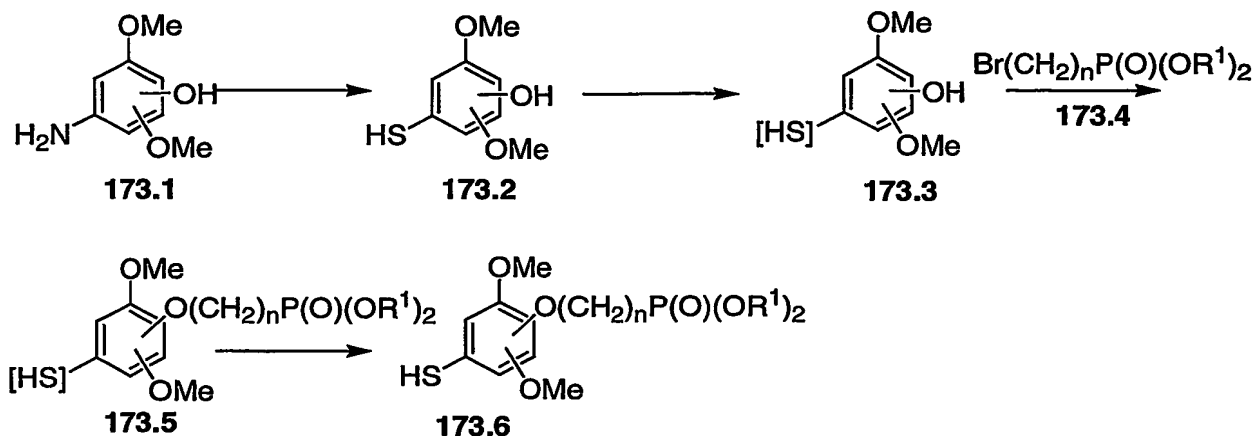
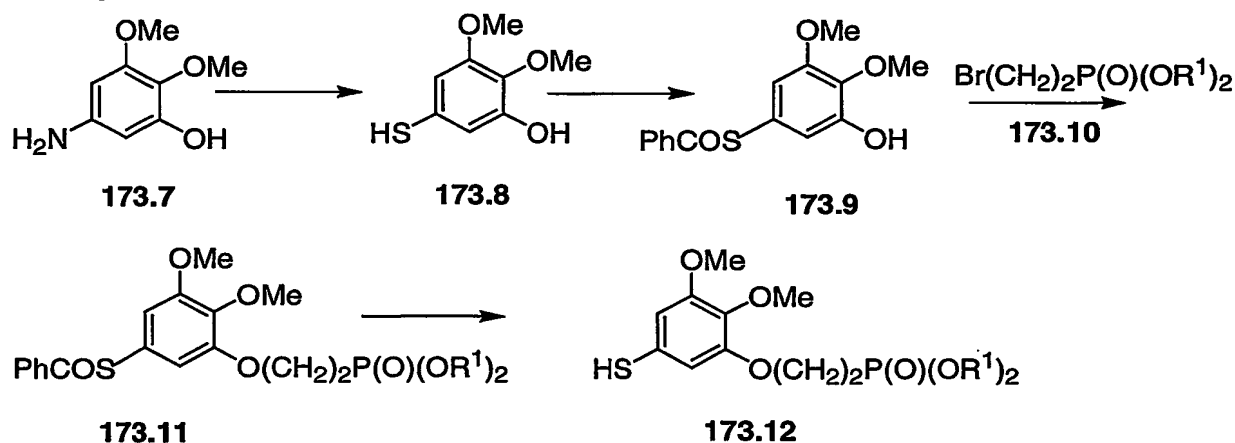
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Scheme 165**Method****Example 1****Example 2****Scheme 166****Method****Example**

Scheme 167**Method****Example 1****Example 2**

Scheme 168**Method****Example 1****Example 2****Scheme 169****Scheme 170****Method****Example 1**

Scheme 171**Method****Example****Scheme 172****Method****Example**

Scheme 173**Method****Example****5 Preparation of ethanolamine derivatives 29.1 incorporating phosphonate groups.**

Schemes 174 - 178 illustrate the preparation of the ethanolamine derivatives 29.1 which are employed in the preparation of the phosphonate esters 18 and 8.

- 10 Scheme 174 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkyl chain. In this procedure, ethanolamine 174.1 is protected to give the derivative 174.2. The product is then reacted with a dialkyl alkyl phosphonate 174.3 in which the alkyl group incorporates a leaving group Lv. The alkylation

reaction is performed in a polar organic solvent such as acetonitrile or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium hexamethyldisilazide, to afford the ether product **174.4**. The protecting group is then removed to yield the amine **174.5**. The protection and deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309. The amino compound **174.5** is then coupled, as described in Scheme 1, with the aminoacid **174.6**, to give the amide **174.7**.

For example, equimolar amounts of phthalimide and ethanolamine are reacted in toluene at 70°C, as described in J. Org. Chem., 43, 2320, 1978, to prepare the phthalimido derivative **174.8**, in which Phth is phthalimido. The product is then reacted, in tetrahydrofuran, with sodium hydride and an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **174.9**, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product **174.10**. The phthalimido group is then removed by treatment of the product **174.10** with ethanolic hydrazine at ambient temperature, as described in J. Org. Chem., 43, 2320, 1978, to yield the amine **174.11**. The product is then coupled, in the presence of dicyclohexylcarbodiimide, with the aminoacid **174.6**, to yield the amide **174.12**. Using the above procedures, but employing, in place of the methylphosphonate **174.9**, different alkylphosphonates **174.3**, the corresponding products **174.7** are obtained.

Scheme 175 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain incorporating a nitrogen. In this procedure, ethanolamine **174.1** and the aminoacid **174.6** are coupled, as described in Scheme 1, to form the amide **175.1**. The product is then alkylated with a bromoalkyl aldehyde **175.2** to yield the ether **175.3**. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dioxan, in the presence of a strong base such as potassium tert. butoxide or sodium hydride, at about 60°C. The aldehyde product is then reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate **175.4**, to produce the amine product **175.5**.

For example, the amide **175.1** is reacted, as described above, with bromoacetaldehyde **175.6**, to afford the ether **175.7**. The product is then reacted in ethanol with a dialkyl aminoethyl phosphonate **175.8**, (Aurora) and sodium triacetoxyborohydride, to yield the amine **175.9**.

Using the above procedures, but employing, in place of the bromoacetaldehyde **175.6**, different bromoalkyl aldehydes **175.2**, and/or different aminoalkyl phosphonates **175.4**, the corresponding products **175.5** are obtained.

- 5 Scheme **176** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of a phenyl ring. In this procedure, bromoethylamine **176.1** and the aminoacid **174.6** are coupled, as described in Scheme **1**, to afford the amide **176.2**. The product is then reacted with the dialkyl hydroxyalkyl-substituted phenylphosphonate **176.3** to prepare the ether **176.4**. The alkylation reaction is performed in a polar organic solvent such as dimethyl sulfoxide or dioxan, in the presence of a base such as lithium bis(trimethylsilyl)amide, sodium hydride or lithium piperidide.
- 10 For example, the amide **176.2** is reacted in dimethylformamide with a dialkyl 4-(2-hydroxyethyl)phenyl phosphonate **176.5**, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, and sodium hydride, to furnish the ether product **176.6**.
- 15 Using the above procedures, but employing, in place of the hydroxyethyl phenylphosphonate **176.5**, different phosphonates **176.3**, the corresponding products **176.4** are obtained.

- Scheme **177** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain. In this procedure, the aminoacid **174.6** is coupled with a bromoalkoxy-substituted ethylamine **177.1** to give the amide **177.2**. The product is then subjected to an Arbuzov reaction with a trialkyl phosphite $P(OR^1)_3$. In this procedure, described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **177.4**.
- 20 For example, the aminoacid **174.6** is coupled, as described in Scheme **1**, in acetonitrile solution containing dicyclohexylcarbodiimide, with 2-bromoethoxyethylamine **177.5**, prepared as described in Vop. Khim. Tekh., 1974, 34, 6, to produce the amide **177.6**. The product is then heated at 120°C with excess trialkyl phosphite **177.3**, to afford the phosphonate **177.7**.
- 25 Using the above procedures, but employing, in place of the bromoethoxyethylamine **177.5**, different bromoalkyl ethylamines **177.1**, the corresponding products **177.4** are obtained.

- 30 Scheme **178** depicts the preparation of the amines **29.1**. The BOC-protected ethanolamine derivatives **178.1**, in which the group A is either the substituent link- $P(O)(OR^1)_2$, or a

precursor thereto, prepared as described in Schemes 174 - 177, are deprotected to afford the amines 29.1. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride in ethyl acetate, or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of the chroman phosphonate esters 33.1.

Schemes 179 - 181a illustrate the preparation of the chroman phosphonate esters 33.1 which are employed in the preparation of the phosphonate esters 17 and 9.

Scheme 179 depicts the preparation of (2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazol-4-yl)-methanol, 179.6, 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carbaldehyde, 179.7, and 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carboxylic acid, 179.8, which are used in the preparation of the phosphonates 33.1. In this procedure, (2H-chromen-2-yl)-methanol 179.1, prepared as described in J. Chem. Soc., (D), 344, 1973, is converted, as described above, (Scheme 1) into the tert. butyldimethylsilyl ether 179.2. The product is then reacted, as described in J. Het. Chem., 1975, 12, 1179, with silver cyanate and iodine in ether, so as to afford the addition product 179.3. This compound is then heated on methanol to yield the carbamate derivative 179.4. The latter compound is heated in xylene at reflux, as described in J. Het. Chem., 1975, 12, 1179, to produce the oxazoline derivative 179.5. The silyl group is then removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran to yield the carbinol 179.6. The carbinol is oxidized to produce the aldehyde 179.7. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, dimethyl sulfoxide/acetic anhydride or dimethyl sulfoxide-dicyclohexyl carbodiimide. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. The aldehyde 179.7 is oxidized to the carboxylic acid 179.8. The oxidation of aldehydes to carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838ff. The conversion is effected by treatment with oxidizing agents such as potassium permanganate,

ruthenium tetroxide, chromium trioxide in acetic acid, or, preferably, by the use of silver oxide, as described in J. Am. Chem. Soc., 73, 2590, 1951.

Scheme 180 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde 179.7 is reacted, under reductive amination conditions, as described in Scheme 175, with a dialkyl aminoalkyl phosphonate 180.1, to give the amine 180.2. The oxazoline group is then hydrolyzed, for example by reaction with aqueous potassium hydroxide, as described in J. Het. Chem., 1975, 12, 1179, to yield the hydroxyamine 180.3.

For example, the aldehyde 179.7 is reacted in ethanol with a dialkyl aminomethyl phosphonate 180.4, (Interchim) and sodium triacetoxyborohydride, to produce the amine 180.5. The oxazoline is then hydrolyzed, as described above, to afford the hydroxyamine 180.6. Using the above procedures, but employing, in place of the aminomethyl phosphonate 180.4, different phosphonates 180.1, the corresponding products 180.3 are obtained.

Scheme 181 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an amide group. In this procedure, the carboxylic acid 179.8 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 180.1, to produce the amide 181.1. Hydrolysis of the oxazoline group, as described above, then yields the hydroxyamine 181.2.

For example, the carboxylic acid 179.8 is coupled with a dialkyl aminopropyl phosphonate 181.3, (Acros) to afford the amide 181.4, which is then hydrolyzed to give the hydroxyamine 181.5.

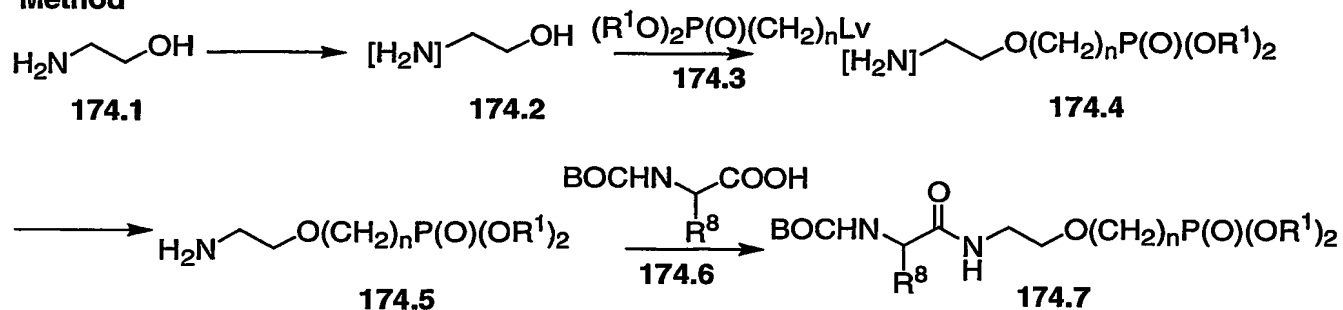
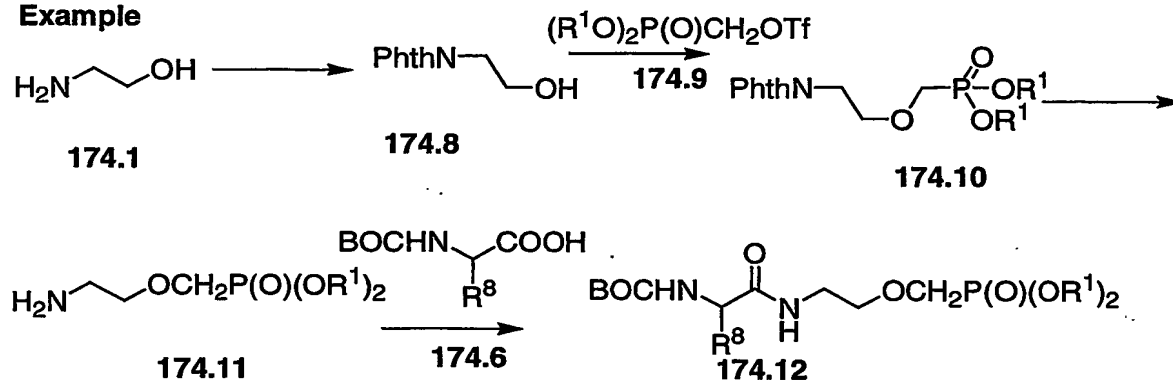
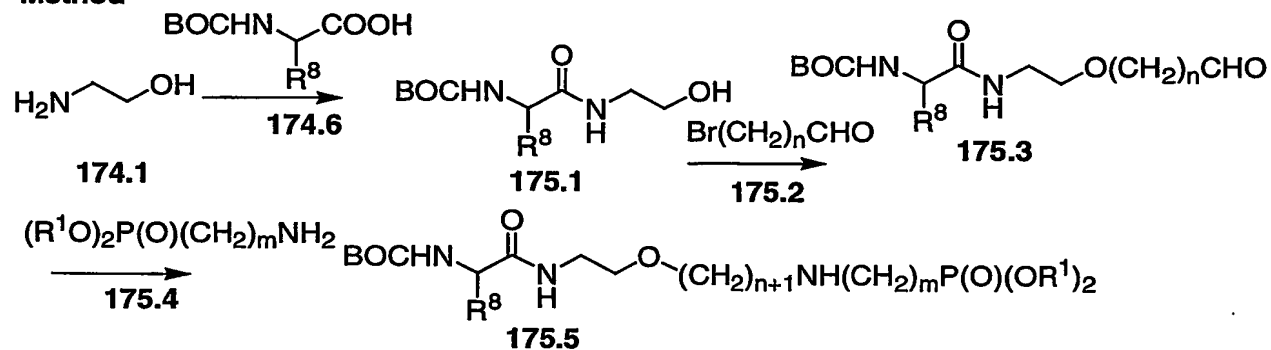
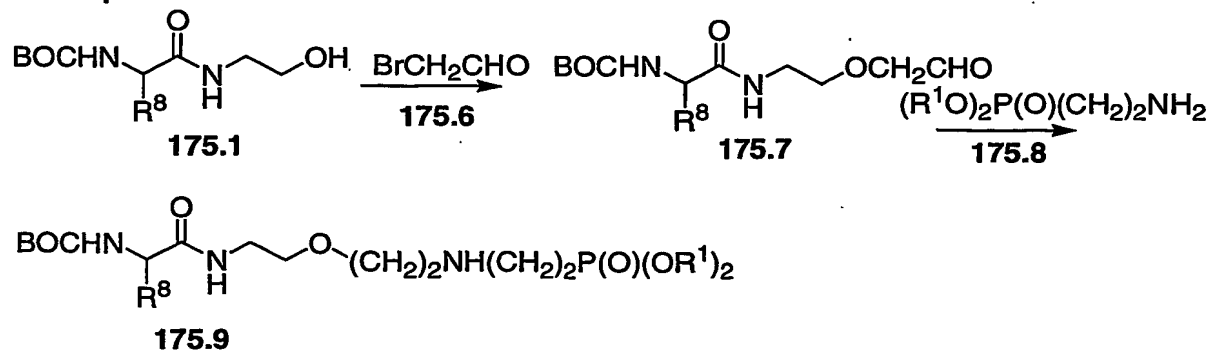
Using the above procedures, but employing, in place of the aminopropyl phosphonate 181.3, different phosphonates 180.1, the corresponding products 181.2 are obtained.

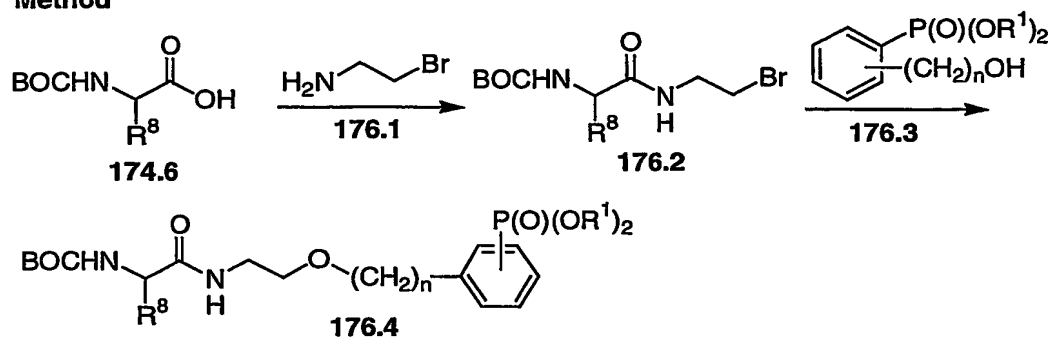
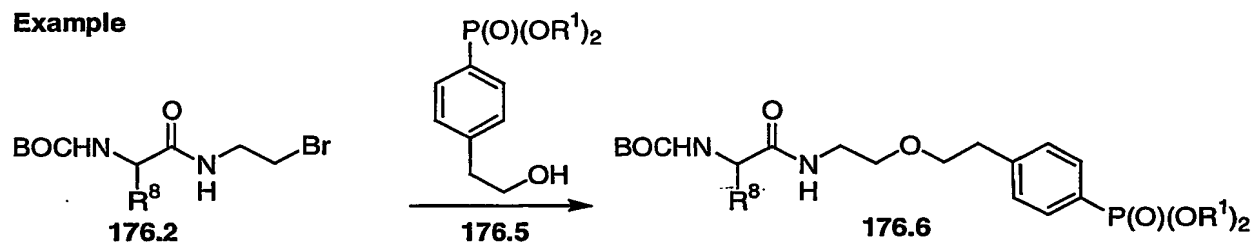
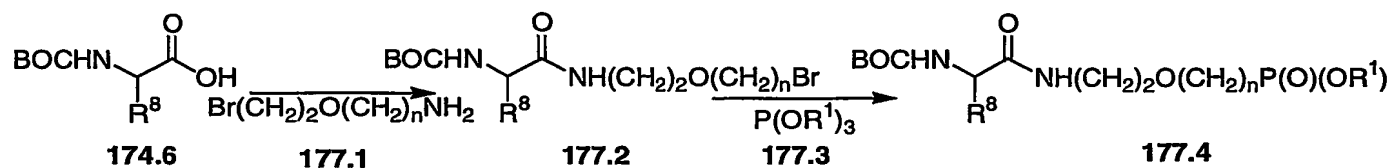
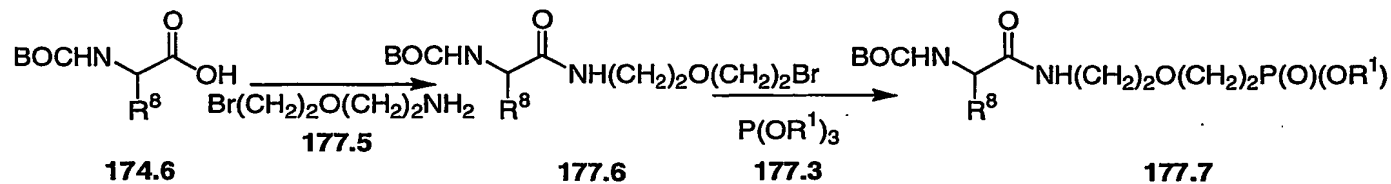
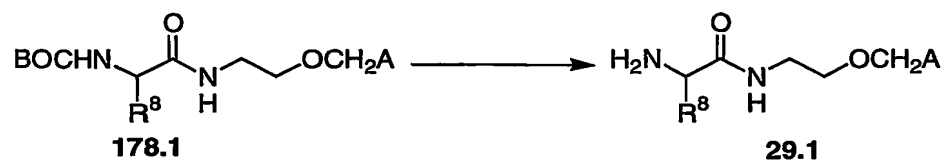
Scheme 181a illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of a thioalkyl group. In this procedure, the carbinol 179.6 is converted into the bromo derivative 181a.1. The conversion of alcohols into bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, the alcohol is reacted with triphenyl phosphine and carbon tetrabromide, trimethylsilyl bromide, thionyl bromide and the like. The bromo compound is

then reacted with a dialkyl thioalkyl phosphonate **181a.2** to effect displacement of the bromide and formation of the thioether **181a.3**. The reaction is performed in a polar organic solvent such as ethanol in the presence of a base such as potassium carbonate. Removal of the isoxazoline group then produces the hydroxyamine **181a.4**.

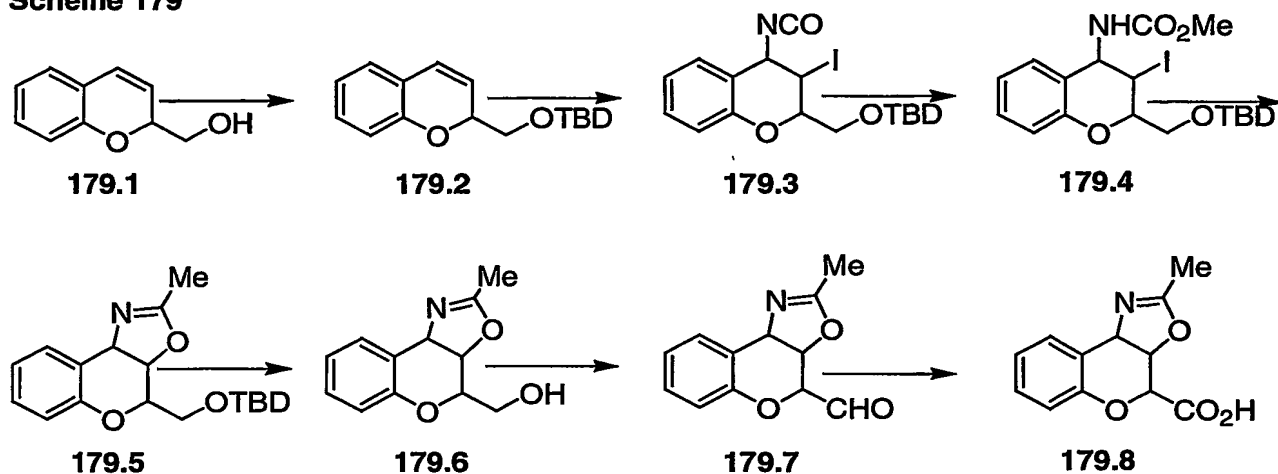
- 5 For example, the bromo compound **181a.1** is reacted in ethanol with a dialkyl thioethyl phosphonate **181a.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **181a.6**. Hydrolysis, as described above, then affords the hydroxyamine **181a.7**.

- 10 Using the above procedures, but employing, in place of the thioethyl phosphonate **181a.5**, different phosphonates **181a.2**, the corresponding products **181a.4** are obtained.

Scheme 174**Method****Example****Scheme 175****Method****Example**

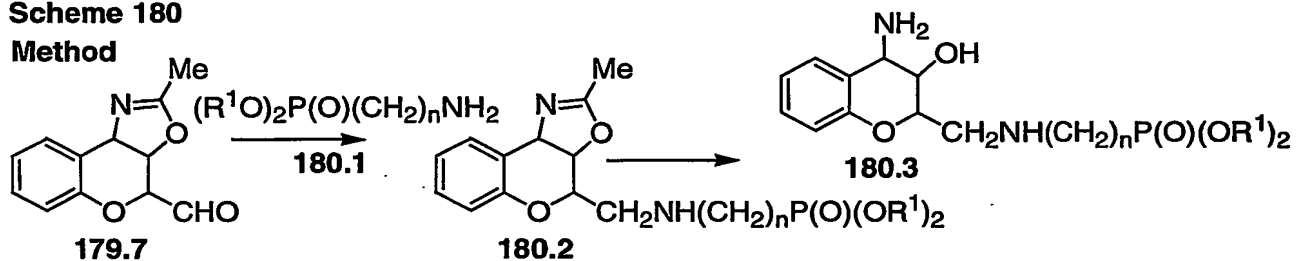
Scheme 176**Method****Example****Scheme 177****Method****Example****Scheme 178**

Scheme 179

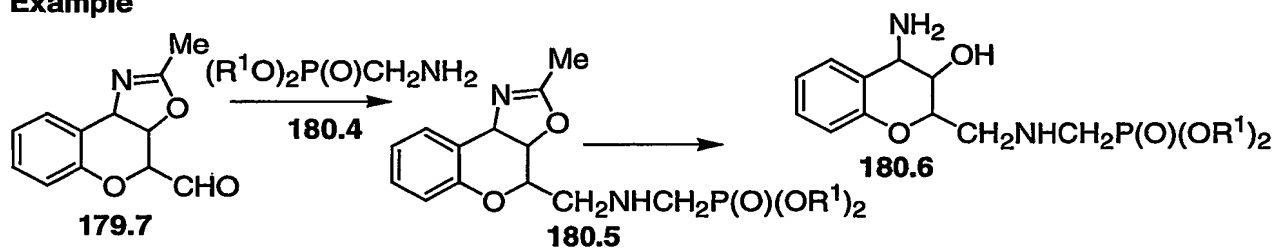


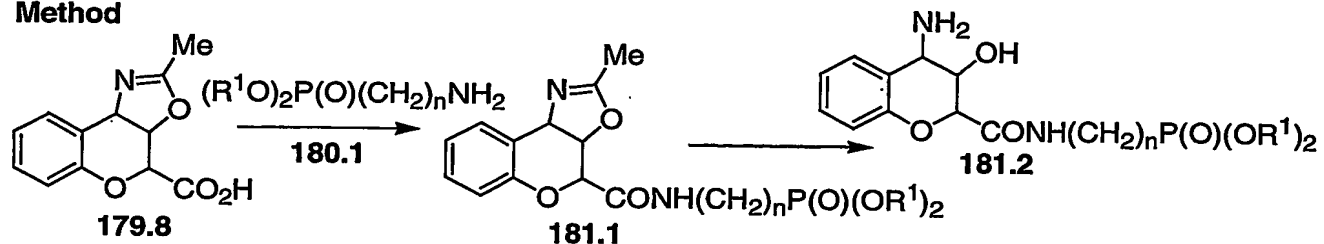
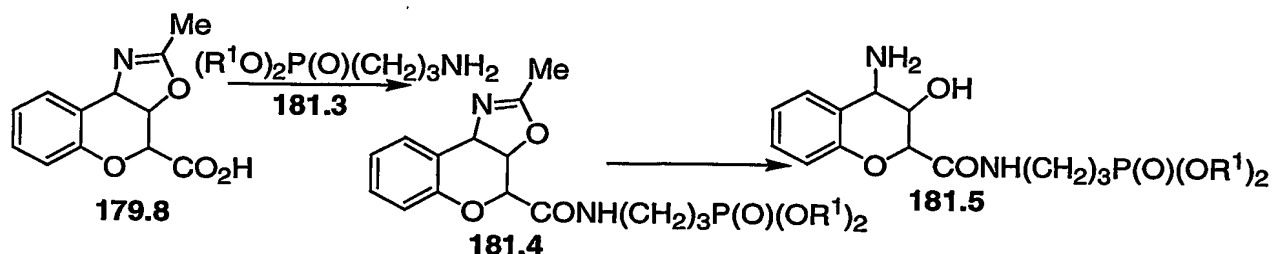
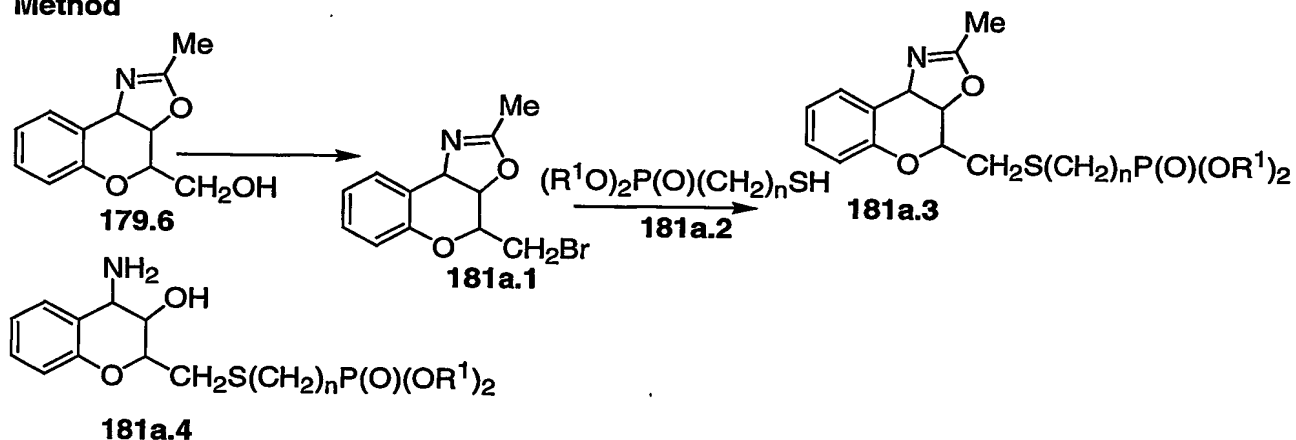
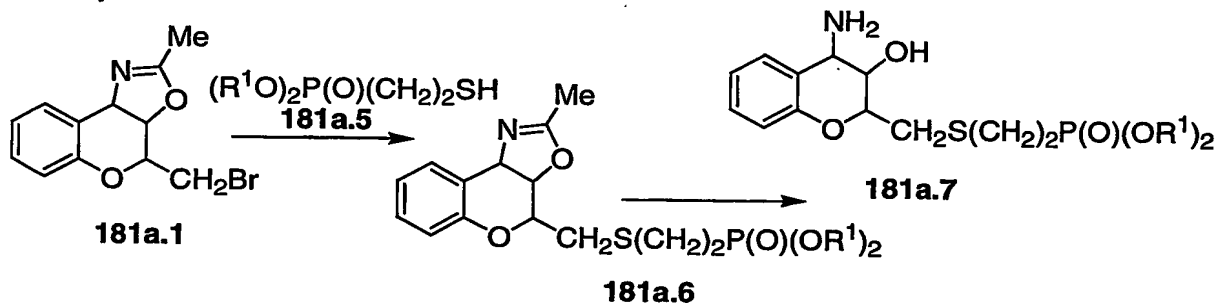
Scheme 180

Method



Example



Scheme 181**Method****Example****Scheme 181a****Method****Example**

Preparation of phenylalanine derivatives 37.1 incorporating phosphonate moieties.

Schemes 182 - 185 illustrate the preparation of phosphonate-containing phenylalanine derivatives 37.1 which are employed in the preparation of the intermediate phosphonate esters 10 and 19.

5

Scheme 182 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 182.1.

- 10 In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 182.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion is effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a
- 15 benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 182.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-
- 20 butyldiphenylsilyl. Thiophenols are also protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 182.3 is then converted into the BOC derivative 182.4. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic
- 25 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups are removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.
- 30 The resultant phenol or thiophenol 182.5 is then reacted under various conditions to provide protected phenylalanine derivatives 182.9, 182.10 or 182.11, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **182.5** is reacted with a dialkyl bromoalkyl phosphonate **182.6** to afford the ether or thioether product **182.9**. The alkylation reaction is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **182.9**. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **182.12**. The benzyl esters **182.10** and **182.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **182**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **182.13** is converted, as described above, into the benzyl ester **182.14**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **182.15**. This compound is then converted, as described above, into the BOC derivative **182.16**. The silyl protecting group is removed by treatment of the silyl ether **182.16** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **182.17**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **182.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **182.19**. Debenzylation then produces the carboxylic acid **182.20**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.13**, different hydroxy or thio-substituted phenylalanine derivatives **182.1**, and/or different bromoalkyl phosphonates **182.6**, the corresponding ether or thioether products

182.12 are obtained.

Alternatively, the hydroxy or mercapto-substituted phenylalanine derivative **182.5** is reacted with a dialkyl hydroxymethyl phosphonate **182.7** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **182.10**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic

solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **182.10**.

For example, as shown in Scheme **182**, Example 2, 3-mercaptophenylalanine **182.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **182.22**.

- 5 The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **182.23**. This compound is then converted into the BOC-protected derivative **182.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **182.24** with mercuric trifluoroacetate and anisole in
- 10 trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **182.25**. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **182.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **182.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **182.27**.
- 15 Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **182.21**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl hydroxymethyl phosphonates **182.7**, the corresponding products **182.10** are obtained.

- Alternatively, the hydroxy or mercapto-substituted protected phenylalanine derivative **182.5** is
- 20 reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **182.8** in which L_v is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **182.11**.

- For example, as illustrated in Scheme **182**, Example 3, 3-hydroxyphenylalanine **182.28** (Fluka)
- 25 is converted, using the procedures described above, into the protected compound **182.29**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **182.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **182.31**. Debenzylation then produces the carboxylic acid **182.32**.

- 30 Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.28**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **182.8**, the corresponding products **182.11** are obtained.

Scheme **183** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted protected phenylalanine derivative **183.3** and a dialkyl aminoalkylphosphonate **183.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **183.1** is converted, as described above, into the BOC protected benzyl ester **183.2**. The latter compound is then oxidized to afford the corresponding aldehyde **183.3**. The conversion of alcohols to aldehydes is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **183.3**. For example, the carbinol **183.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the aldehyde **183.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **183.4** in the presence of a suitable reducing agent to afford the amine product **183.5**. The preparation of amines by means of reductive amination procedures is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, p. 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **183.6**.

For example, 3-(hydroxymethyl)-phenylalanine **183.7**, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated derivative **183.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **183.9**, prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **183.10**, which is then deprotected to give the carboxylic acid **183.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **183.7**, different hydroxymethyl phenylalanines **183.1**, and/or different aminoalkyl phosphonates **183.4**, the corresponding products **183.6** are obtained.

- 5 Scheme **184** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **184.1** is converted, as described above, (Scheme **182**) into the protected derivative **184.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **184.3** to produce the phosphonate ester **184.4**. The preparation of
10 arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid **184.5**.

For example, 3-bromophenylalanine **184.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **182**) into the protected compound **184.7**. This
15 compound is then reacted, in toluene solution at reflux, with diethyl phosphite **184.8**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **184.9**. Debenzylation then yields the carboxylic acid **184.10**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **184.6**, different
20 bromophenylalanines **184.1**, and/or different dialkylphosphites **184.3**, the corresponding products **184.5** are obtained.

Scheme **185** depicts the preparation of the aminoacid derivative **37.1** which is employed in the preparation of the phosphonate esters **10** and **19**. In this procedure, the BOC-protected
25 phenylalanine derivatives **185.1**, in which the substituent A is the group link-P(O)(OR¹)₂ or a precursor group, the preparation of which is described in Schemes **182 – 184**, is converted into the esters or amides **185.2** in which R⁹ is morpholino or alkoxy. The transformation is accomplished by coupling the acid, as described in Scheme **1**, with morpholine or an alkanol in the presence of a carbodiimide. The product **185.2** is then deprotected to afford the free
30 amine **185.3**, for example as described in Scheme **3**. The amine **185.3** is then coupled, as described in Scheme **1**, with the aminoacid **174.6**, to give the amide **185.4**. The BOC group is then removed, as described in Scheme **49**, to produce the amine **37.1**.

Preparation of the dimethoxyphenylpropionic esters 21.1 incorporating phosphonate groups.

Scheme 186 illustrates the preparation of the dimethoxyphenylpropionic acid derivatives 21.1 which are employed in the preparation of the phosphonate esters 6. In this procedure, the dimethoxybenzyl alcohol derivative 186.1, in which the substituent A is the group link-
P(O)(OR¹)₂ or a precursor group, the preparation of which is described in Schemes 165 – 168, is converted into the corresponding aldehyde 186.2. The oxidation is effected as described in Scheme 175. The aldehyde is then subjected to a Wittig reaction with methyl
triphenylphosphoranylideneacetate 138.2, as described in Scheme 138, to generate the cinnamic ester derivative 186.3. The double bond is then reduced, as described in Scheme 138, to afford the phenylpropionic ester 21.1. Alternatively, the dimethoxybenzyl bromide derivative 186.4, the preparation of which is described in Scheme 169, is reacted, as described in Scheme 138, with dimethyl malonate 186.5 to yield the malonic ester derivative 186.6, which is then transformed, as described in Scheme 138, into the ester 21.1.

Preparation of the phosphonate-containing benzyl iodides 58.1 and benzylcarbamates 125.3.

Schemes 187 - 191 illustrate methods for the preparation of the benzyl iodide derivatives 58.1 which are employed in the synthesis of the phosphonate esters 14, and of the benzyl carbamates 125.3 which are employed in the preparation of the phosphonate esters 22.

Scheme 187 illustrates the preparation of benzaldehyde phosphonates 187.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 187.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 187.2, under reductive amination conditions, as describe above in Scheme 135, to yield the phosphonate product 187.3.

For example, benzene-1,3-dialdehyde 187.4 is reacted with a dialkyl aminopropyl phosphonate 187.5, (Acros) and sodium triacetoxyborohydride, to afford the product 187.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **187.4**, different benzene dialdehydes **187.1**, and/or different phosphonates **187.2**, the corresponding products **187.3** are obtained.

5 Scheme **188** illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde **188.1** is coupled, under palladium catalysis as described in Scheme **150**, with a dialkyl alkenylphosphonate **188.2**, to afford the alkenyl phosphonate **188.3**. Optionally, the product is reduced, as described in Scheme **150**, to afford the saturated
10 phosphonate ester **188.4**. Alternatively, the bromobenzaldehyde is coupled, as described in Scheme **144**, with a dialkyl phosphite **188.5** to afford the formylphenylphosphonate **188.6**. For example, as shown in Example **1**, 3-bromobenzaldehyde **188.7** is coupled with a dialkyl propenylphosphonate **188.8** (Aldrich) to afford the propenyl product **188.9**. Optionally, the product is reduced, as described in Scheme **150**, to yield the propyl phosphonate **188.10**.

15 Using the above procedures, but employing, in place of 3-bromobenzaldehyde **188.7**, different bromobenzaldehydes **188.1**, and/or different alkenyl phosphonates **188.2**, the corresponding products **188.3** and **188.4** are obtained.

Alternatively, as shown in Example **2**, 4-bromobenzaldehyde **188.11** is coupled, as described in Scheme **144**, with a dialkyl phosphite **188.5** to afford the 4-formylphenyl phosphonate
20 product **188.12**.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde **188.11**, different bromobenzaldehydes **188.1**, the corresponding products **188.6** are obtained.

Scheme **189** illustrates the preparation of formylphenyl phosphonates in which the
25 phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine **189.1** is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate **189.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **189.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or
30 acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **189.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium

hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **189.4**, prepared as described in *Macromolecules*, 1991, 24, 1710, is reacted in acetonitrile at 60°C with one molar equivalent of a dialkyl

5 iodomethyl phosphonate **189.5**, (Lancaster) to give the ether product **189.6**.

Using the above procedures, but employing, in place of the carbinol **189.4**, different carbinols, thiols or amines **189.1**, and/or different haloalkyl phosphonates **189.2**, the corresponding products **189.3** are obtained.

10 Scheme **190** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **190.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **190.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to
15 afford diaryl compounds is described in *Palladium Reagents and Catalysts*, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **190.3** is then coupled, as described above (Scheme **144**) with a dialkyl phosphite **190.4** to afford the phosphonate **190.5**.

20 For example, 4-formylbenzeneboronic acid **190.6** is coupled with 2,5-dibromothiophene **190.7** to yield the phenylthiophene product **190.8**. This compound is then coupled with the dialkyl phosphite **190.4** to afford the thienyl phosphonate **190.9**.

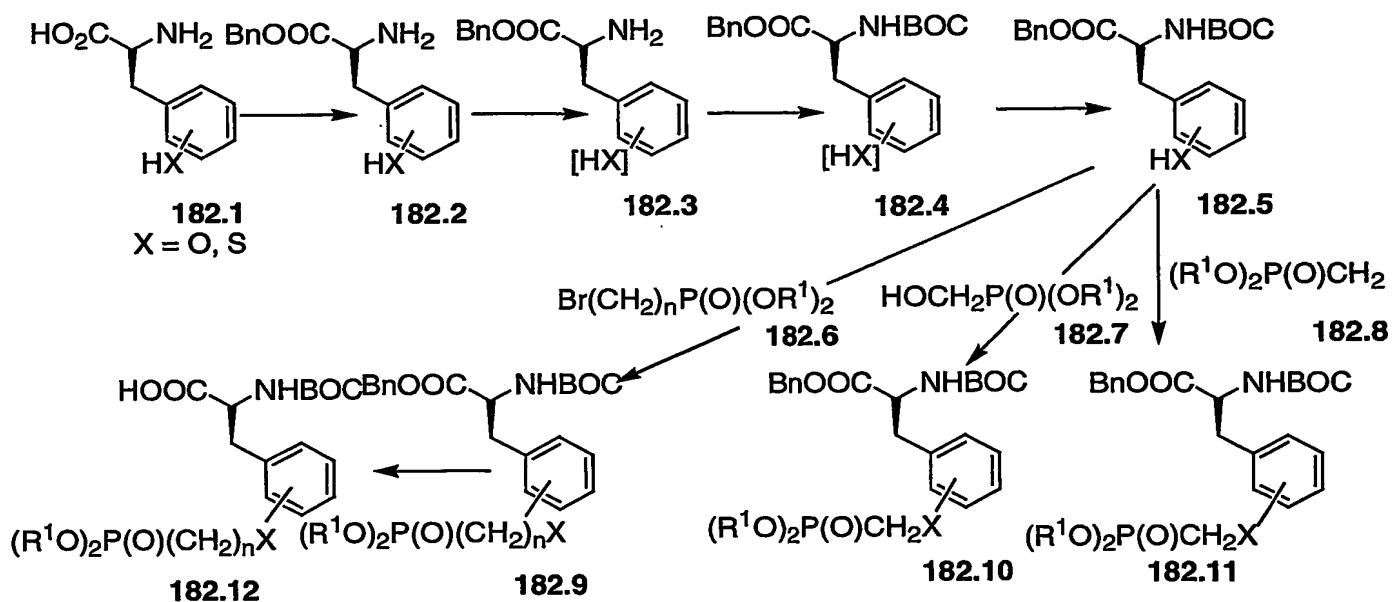
Using the above procedures, but employing, in place of dibromothiophene **190.7**, different dibromoarenes **190.2**, and/or different formylphenyl boronates **190.1**, the corresponding
25 products **190.5** are obtained.

Scheme **191** illustrates the preparation of the benzyl carbamates **125.3** and the benzyl iodides **58.1**, which are employed respectively in the preparation of the phosphonate esters **22** and **4**. In this procedure, the substituted benzaldehydes **191.1**, prepared as shown in Schemes **187** –
30 **190**, are converted into the corresponding benzyl alcohols **191.2**. The reduction of aldehydes to afford alcohols is described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the use of reducing agents such as

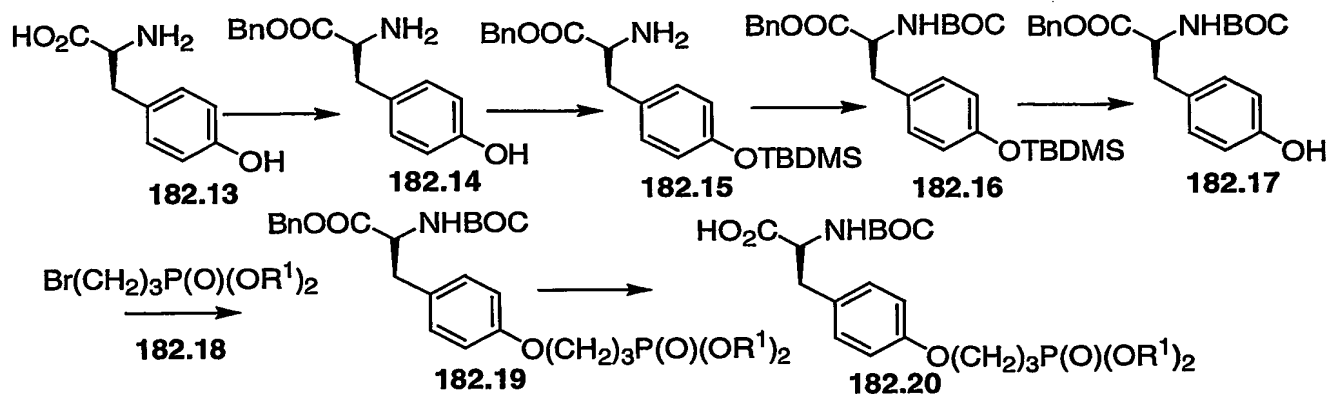
sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **191.3** to afford the carbamate **191.4**. The reaction is performed under the conditions described below, Scheme **198**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce
5 an intermediate benzyloxycarbonyl imidazole, and the intermediate is reacted with the aminoester **191.3** to afford the carbamate **191.4**. The methyl ester is then hydrolyzed, as described in Scheme **3**, to yield the carboxylic acid **125.3**. Alternatively, the benzyl alcohol **191.2** is converted, using the procedures of Scheme **169**, into the iodide **58.1**.

Scheme 182

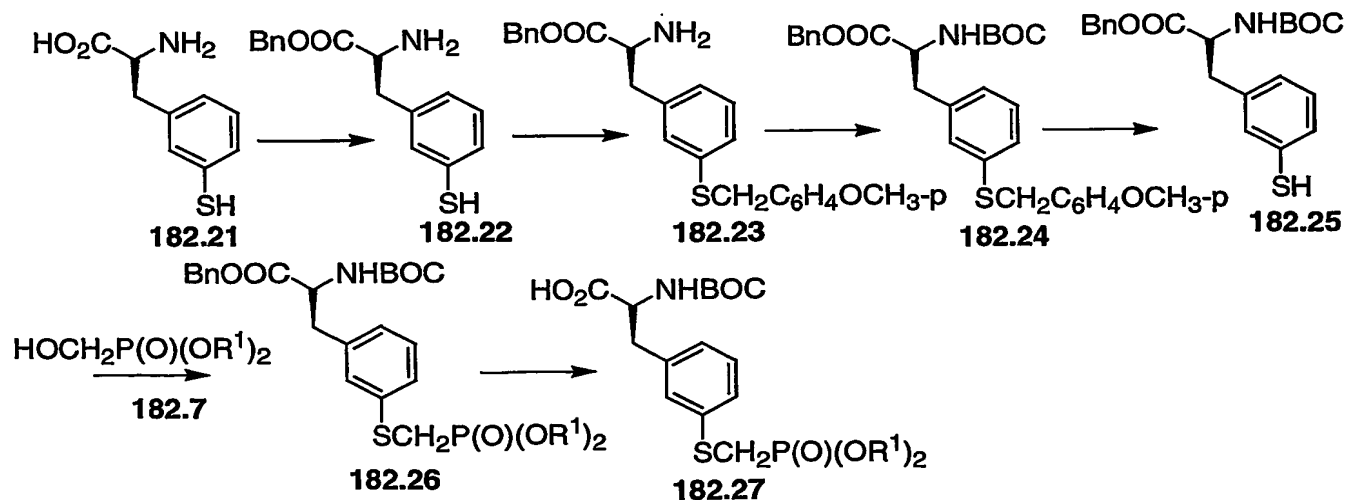
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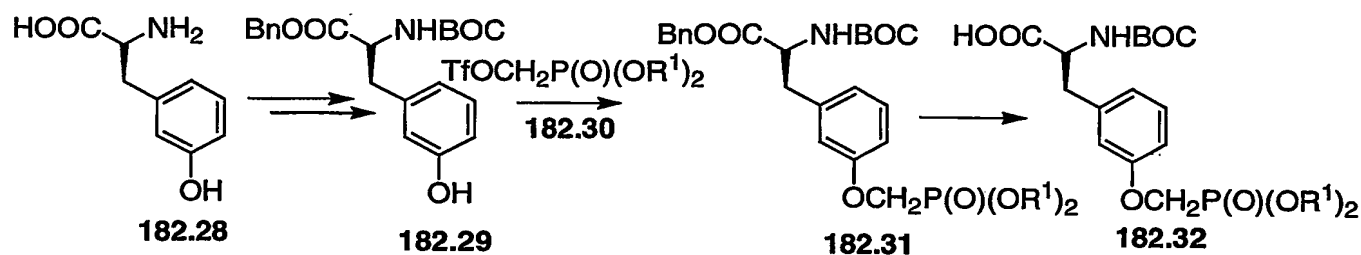
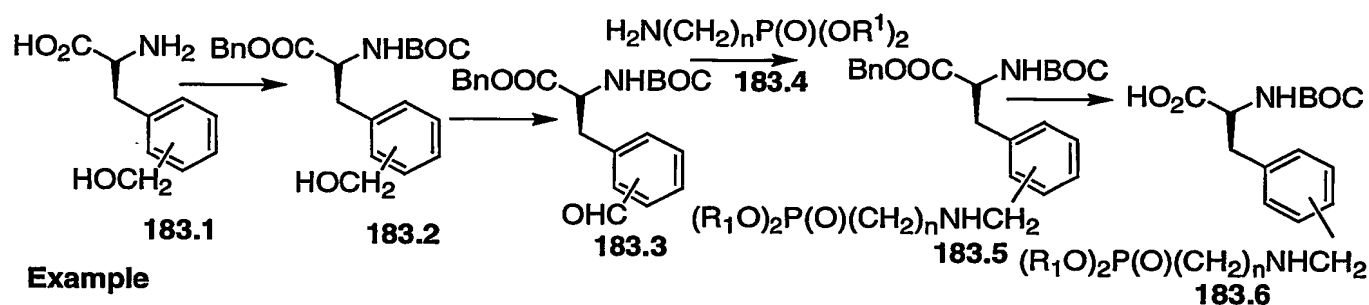
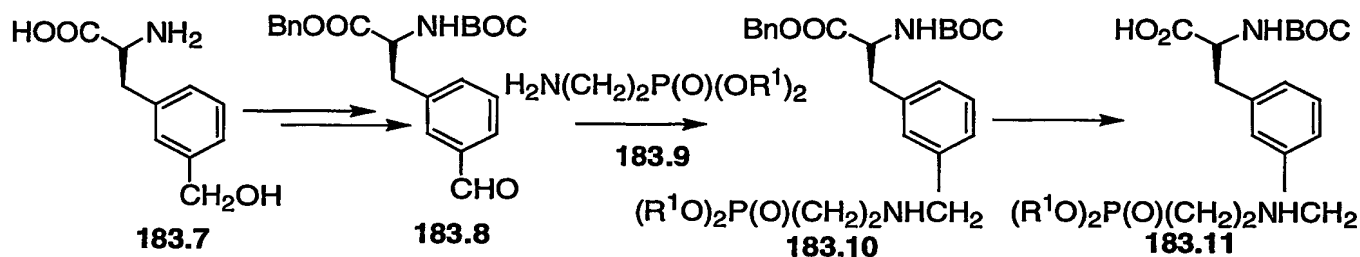
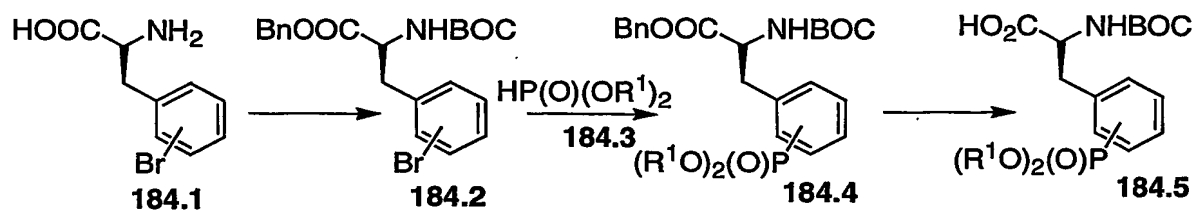
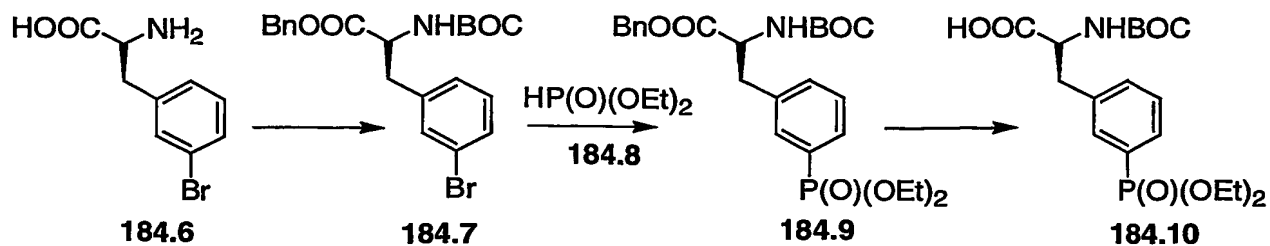


Example1

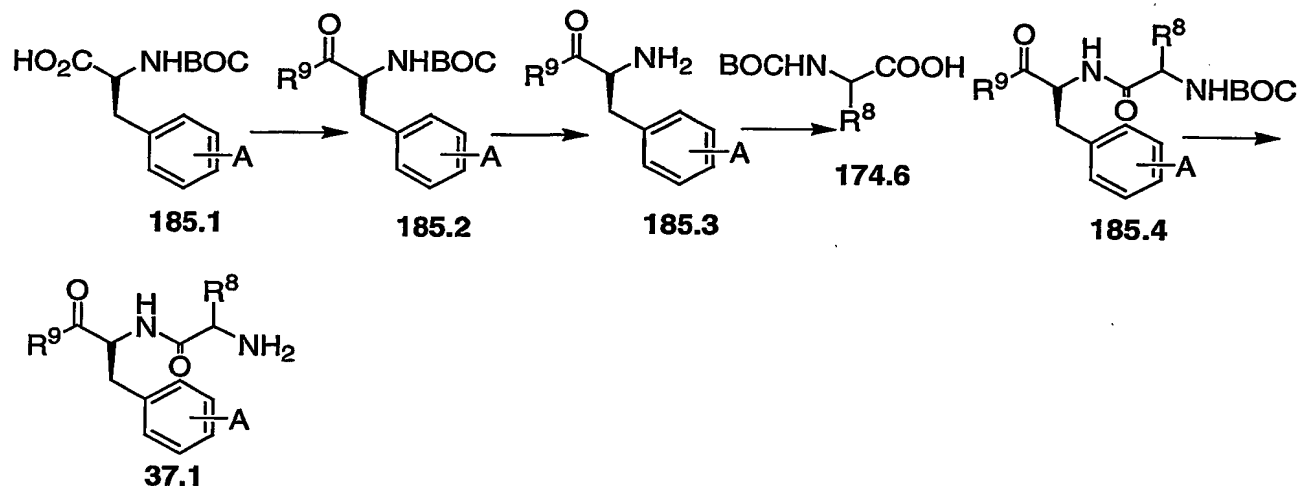


Example 2

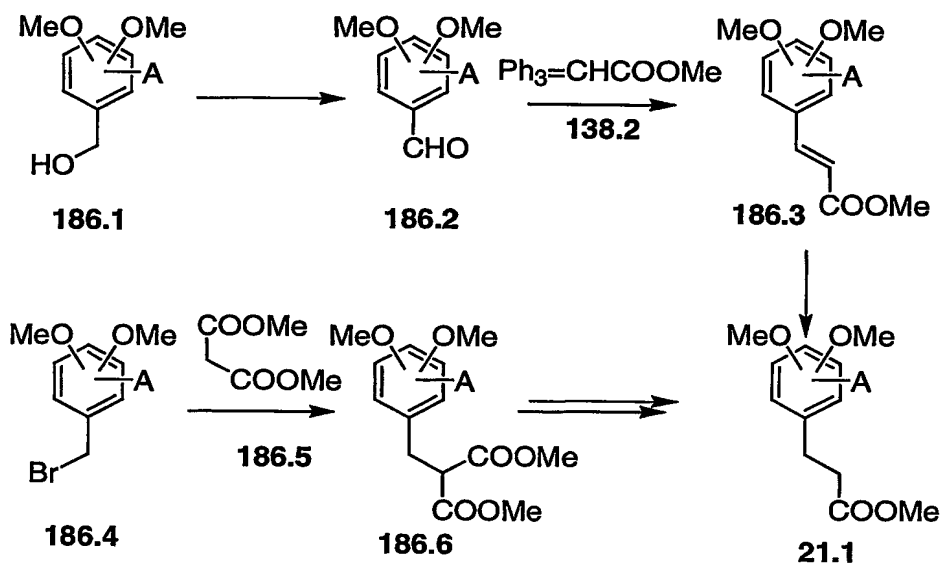


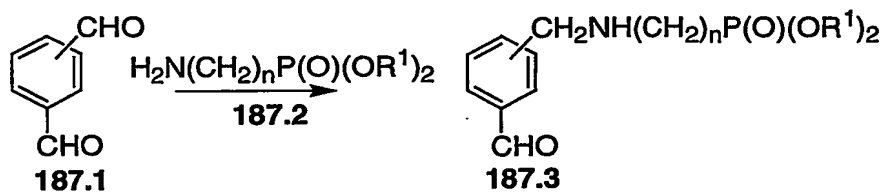
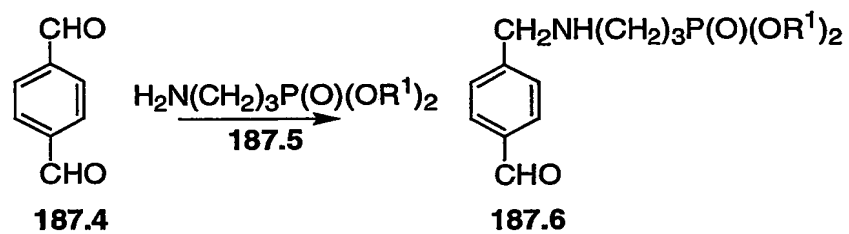
Example 3**Scheme 183**
Method**Example****Scheme 184****Example**

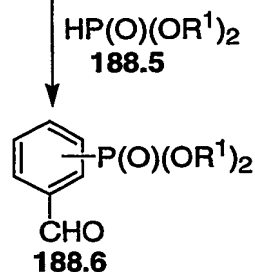
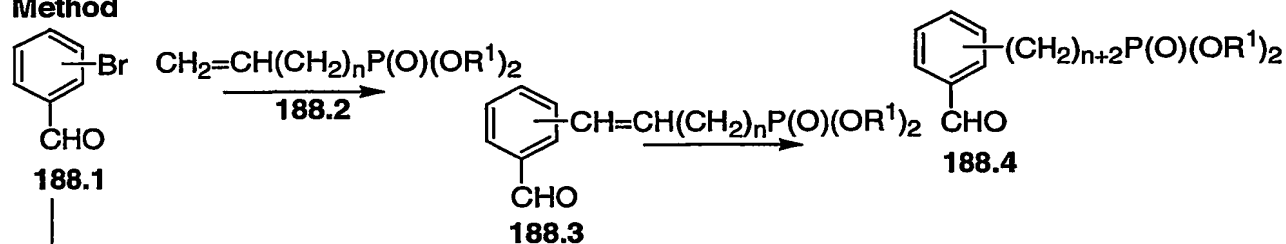
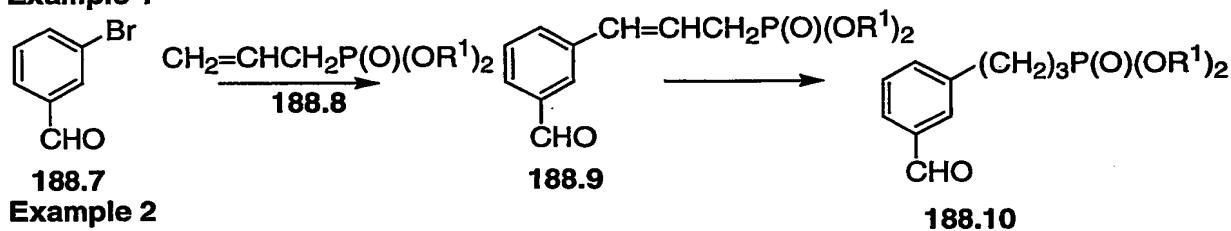
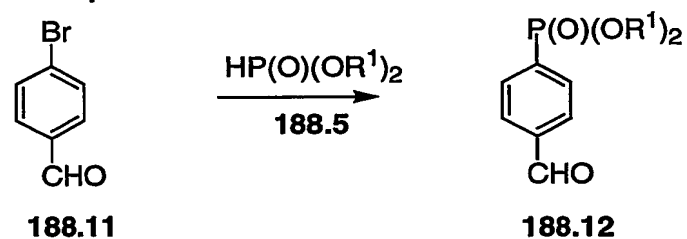
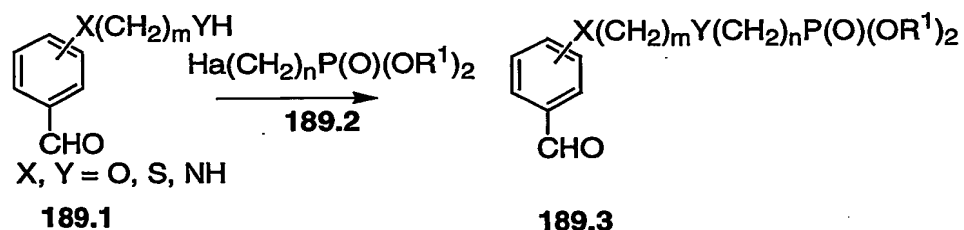
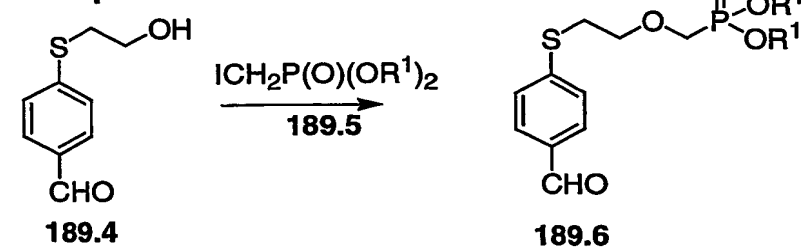
Scheme 185

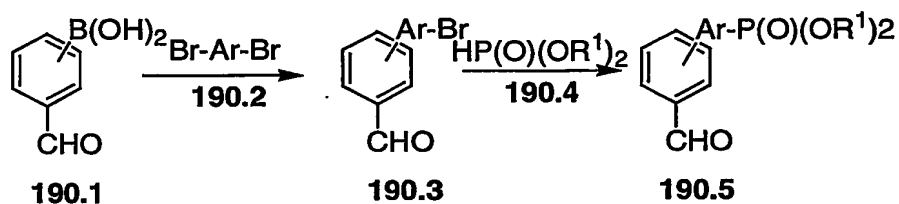
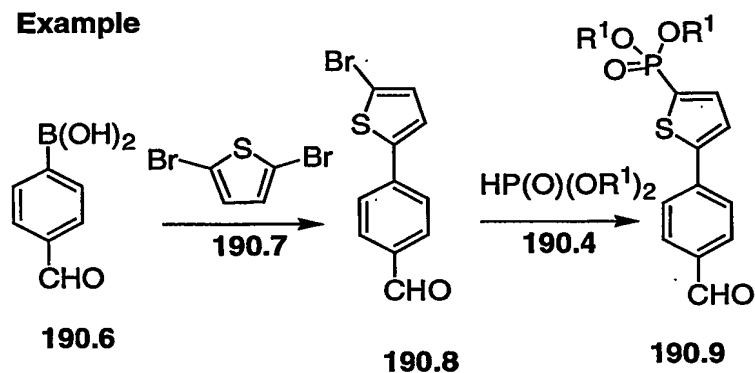
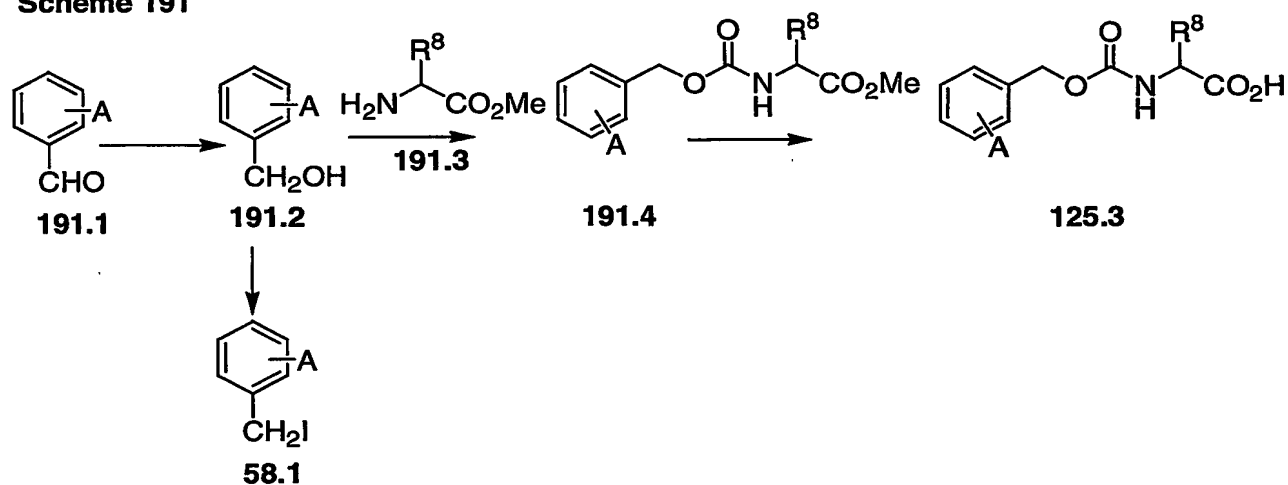


Scheme 186



Scheme 187**Method****Example**

Scheme 188**Method****Example 1****Example 2****Scheme 189****Method****Example**

Scheme 190**Method****Example****Scheme 191****5 Preparation of phosphonate-substituted decahydroquinolines 17.1.**

Schemes 192 – 97 illustrate the preparation of decahydroisoquinoline derivatives 17.1 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br.

The compounds are employed in the preparation of the intermediate phosphonate esters **5**, **12** and **21**.

Scheme **192** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate **192.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **192.1**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **192.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **192.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **192.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **192.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **192.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **192.4** is obtained from 2-hydroxyphenylalanine **192.5**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **192.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **192.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **192.6**. The reduction is also performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **192.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline **192.6**.

Protection of the carboxyl and NH groups present in **192.6**, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **192.9**, in which R is trichloroethyl and R¹ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butoxy aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol **192.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **192.10**.

The alcohol **192.6** is converted into the thiol **192.13** and the amine **192.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry.

For example, the alcohol **192.6** is converted into an activated ester such as the trifluoromethanesulfonyloxy ester or the methanesulfonate ester **192.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **192.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **192.13**.

For example, the mesylate **192.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **192.12**, in which R is COCH₃. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **192.13**.

The mesylate **192.7** is treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine **192.14**.

For example, the mesylate **192.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **192.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **192.14**.

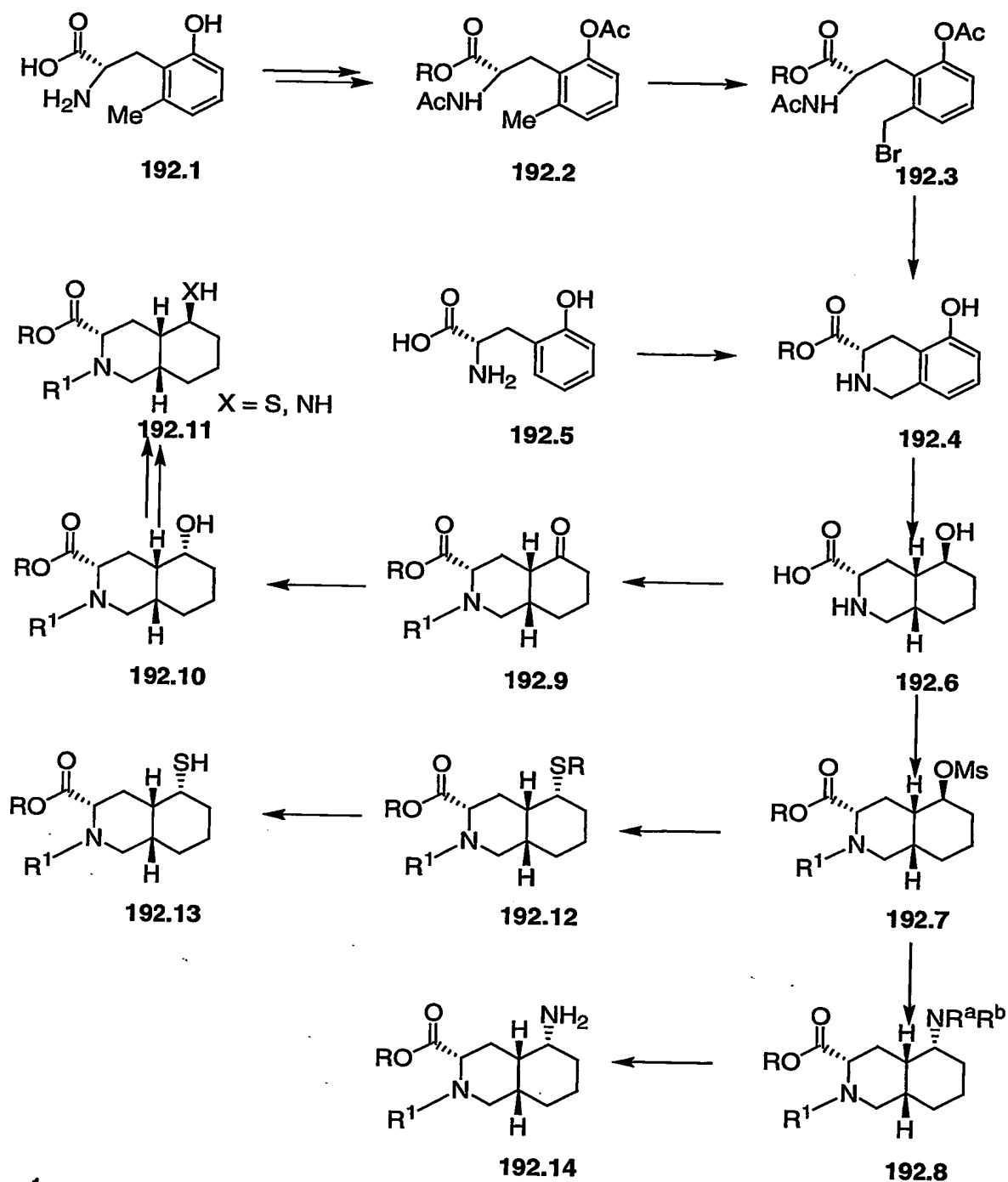
- 5 The application of the procedures described above for the conversion of the β -carbinol **192.6** to the α -thiol **192.13** and the α -amine **192.14** can also be applied to the α -carbinol **192.10**, so as to afford the β -thiol and β -amine, **192.11**.

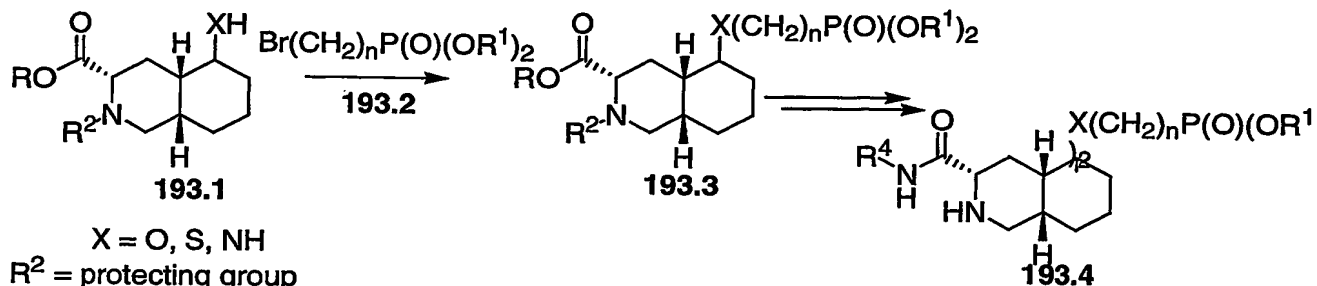
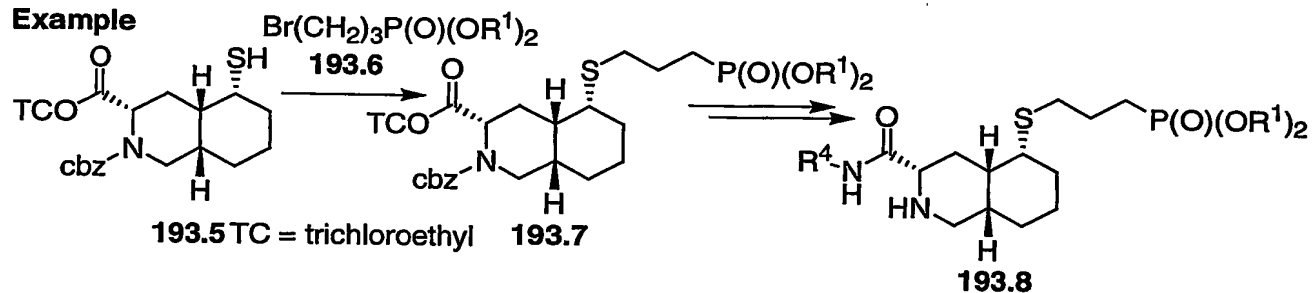
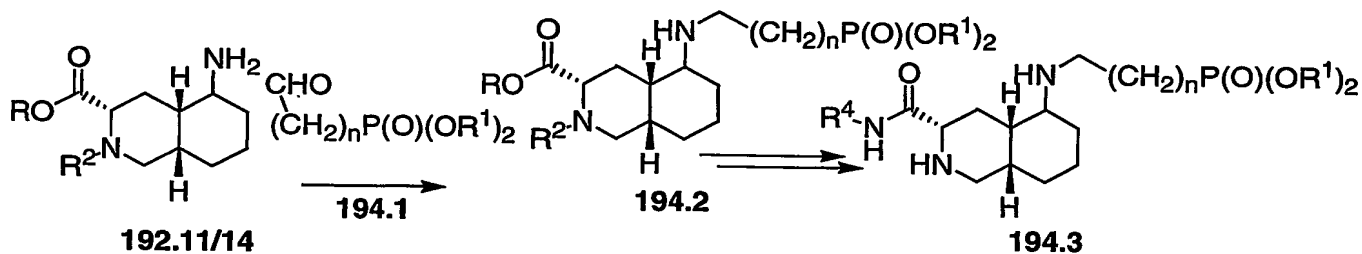
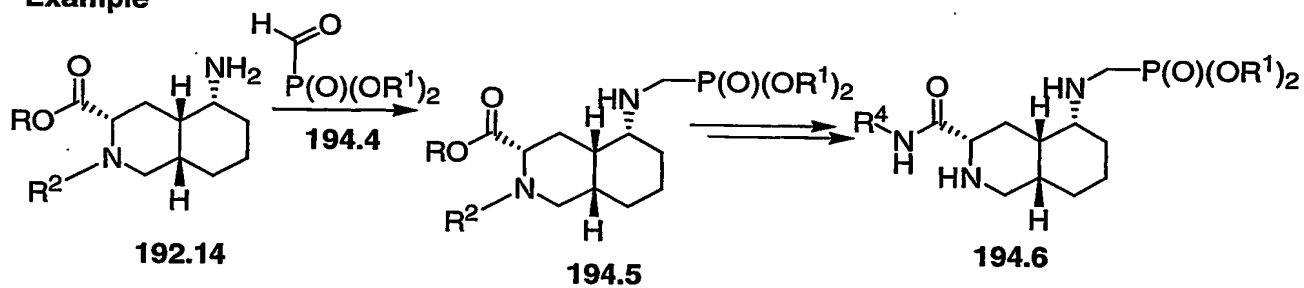
- 10 Scheme **193** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain. In this procedure, an alcohol, thiol or amine **193.1** is reacted with a bromoalkyl phosphonate **193.2**, under the conditions described above for the preparation of the phosphonate **155.4** (Scheme **155**), to afford the displacement product **193.3**. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described
15 below, (Scheme **197**) then yields the amine **193.4**.

- For example, the thiol **193.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **193.6**, the preparation of which is described in J.
20 Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product **193.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **193.8**.

- Using the above procedures, but employing, in place of the α -thiol **193.5**, the alcohols, thiols or amines **192.6**, **192.10**, **192.11**, **192.13**, **192.14**, of either α - or β -orientation, there are
25 obtained the corresponding products **193.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 192



Scheme 193**Method****Example****Scheme 194****Method****Example**

Scheme 194 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **192.14** or **192.11** are reacted with a phosphonate aldehyde **194.1**, in the presence of a reducing agent, to afford the alkylated amine **194.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **194.3**.

- 5 For example, the protected amino compound **192.14** is reacted with a dialkyl formylphosphonate **194.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **194.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **194.6**.
10 Using the above procedures, but employing, instead of the α -amine **192.14**, the β isomer, **192.11** and/or different aldehydes **194.1**, there are obtained the corresponding products **194.3**, in which the orientation of the side chain is the same as that of the amine precursor.

- 15 Scheme **195** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain. In this procedure, a dialkyl mercaptoalkyl phosphonate **195.2** is reacted with a mesylate **195.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **195.3**. Deprotection of the ester group, followed by conversion of the acid
20 to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.4**.

- For example, the protected mesylate **195.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **195.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the
25 presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thioether phosphonate **195.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.8**

- Using the above procedures, but employing, instead of the phosphonate **195.6**, different
30 phosphonates **195.2**, there are obtained the corresponding products **195.4**.

Scheme 196 illustrates the preparation of decahydroisoquinoline phosphonates 196.4 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 196.1 and a bromomethyl-substituted arylphosphonate 196.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 196.1. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate is employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is employed. The displacement reaction affords the ether, thioether or amine compounds 196.3. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.4.

For example, the alcohol 196.5 is reacted at ambient temperature with a dialkyl 3-bromomethyl benzylphosphonate 196.6, the preparation of which is described above, (Scheme 143). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate 196.6, to afford the product 196.7. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.8.

Using the above procedures, but employing, instead of the β -carbinol 196.5, different carbinols, thiols or amines 196.1, of either α - or β -orientation, and/or different phosphonates 196.2, in place of the phosphonate 196.6, there are obtained the corresponding products 196.4 in which the orientation of the side-chain is the same as that of the starting material 196.1.

Schemes 193 - 196 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 197 illustrates the conversion of the latter group of compounds 197.1 (in which the group A is link-P(O)(OR¹)₂ or optionally protected precursor substituents, such as, for example, OH, SH, or NH₂ to the corresponding R⁴NH amides 17.1.

As shown in Scheme 197, the ester compounds 197.1 are deprotected to form the corresponding carboxylic acids 197.2. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and

the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **197.2** to the R⁴NH amide **197.4** is then accomplished by reaction, as described in Scheme 1, of the carboxylic acid, or an activated derivative thereof, with the amine R⁴NH₂ (**197.3**) to afford the amide **197.4**. Deprotection of the NR² group, as described above, then affords the free amine **17.1**.

Preparation of carbamates.

- 10 The phosphonate esters **13 - 20** in which the R¹⁰ is alkoxy, and the phosphonate esters **22** contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
- 15 Scheme **198** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **198**, in the general reaction generating carbamates, a carbinol **198.1**, is converted into the activated derivative **198.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **198.2** is then reacted with an amine **198.3**, to afford the carbamate product **198.4**. Examples **1 - 7** in
- 20 Scheme **198** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.
- Scheme **198**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **198.1**. In this procedure, the carbinol is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965,
- 25 or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **198.6**. The latter compound is then reacted with the amine component **198.3**, in the presence of an organic or inorganic base, to afford the carbamate **198.7**. For example, the chloroformyl compound **198.6** is reacted with the amine **198.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of
- 30 aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **198.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 198, Example 2 depicts the reaction of the chloroformate compound 198.6 with imidazole to produce the imidazolid 198.8. The imidazolid product is then reacted with the amine 198.3 to yield the carbamate 198.7. The preparation of the imidazolid is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 198 Example 3, depicts the reaction of the chloroformate 198.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 198.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 198.19 - 198.24 shown in Scheme 198, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 198.19, N-hydroxysuccinimide 198.20, or pentachlorophenol, 198.21, the mixed carbonate 198.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 198.22 or 2-hydroxypyridine 198.23 is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 198 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 198.8 is employed. In this procedure, a carbinol 198.5 is reacted with an equimolar amount of carbonyl diimidazole 198.11 to prepare the intermediate 198.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 198.8 is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate 198.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 198.7.

Scheme 198, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonylbenztriazole 198.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 198.12, to afford the alkoxy carbonyl product 198.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine R'NH₂ to afford the

carbamate **198.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **198**, Example **6** illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, **198.14**, is reacted with a carbinol **198.5** to afford the intermediate

- 5 alkyloxycarbonyl intermediate **198.15**. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate **198.7**. The procedure in which the reagent **198.15** is derived from hydroxybenztriazole **198.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **198.15** is derived from N-hydroxysuccinimide **198.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **198.15** is derived from 2-hydroxypyridine
- 10 **198.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **198.15** is derived from 4-nitrophenol **198.24** is described in Syn. 1993, 199. The reaction between equimolar amounts of the carbinol ROH and the carbonate **198.14** is conducted in an inert organic solvent at ambient temperature.

- Scheme **198**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides
- 15 **198.16**. In this procedure, an alkyl chloroformate **198.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **198.16**. The latter compound is then reacted with an equimolar amount of the amine R'NH₂ to afford the carbamate **198.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

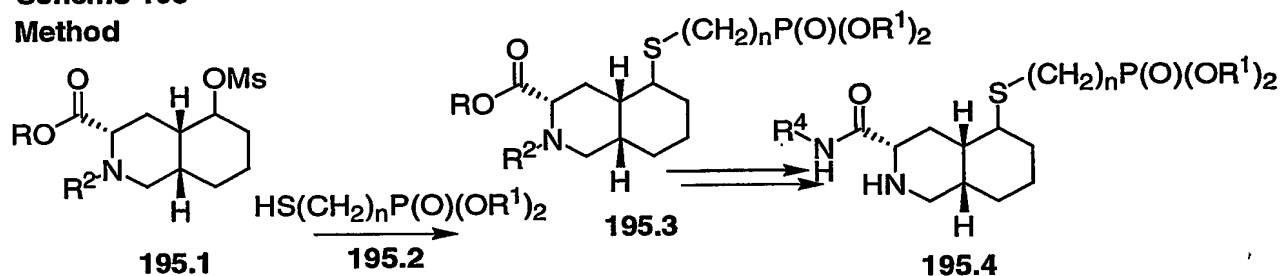
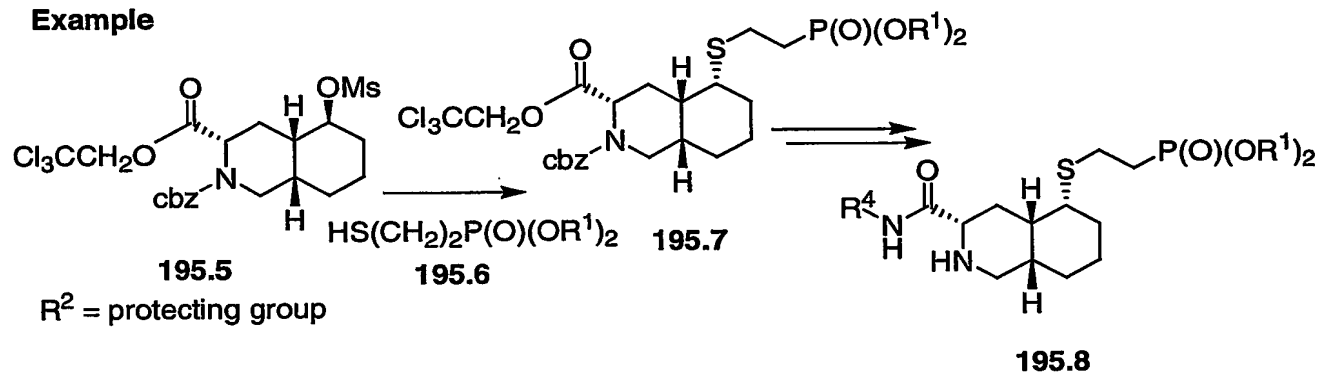
- 20 Scheme **198**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **198.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate
- 25 **198.7**.

- Scheme **198**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **198.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane
- 30 and the like, to afford the carbamate **198.7**.

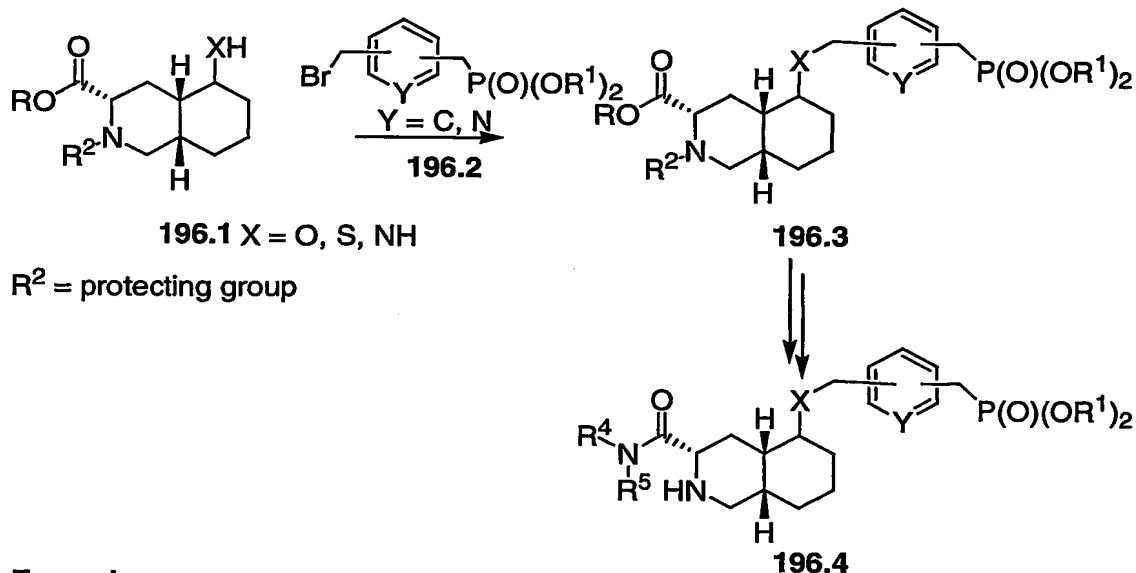
Scheme **198**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine R'NH₂. In this procedure, which is described in Chem.

Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **198.7**.

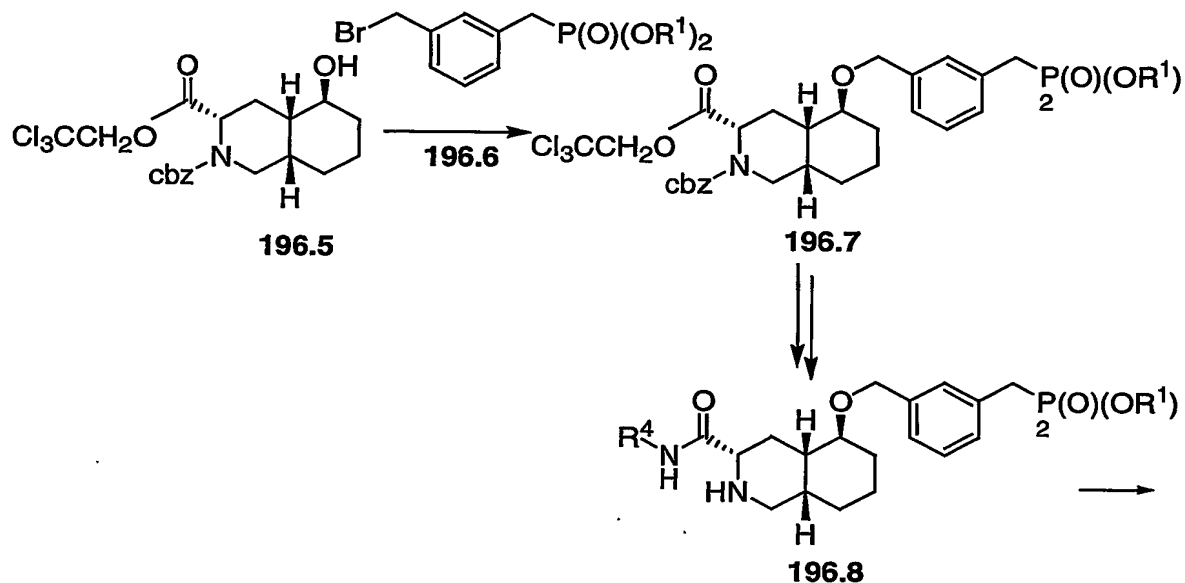
5

Scheme 195**Method****Example**

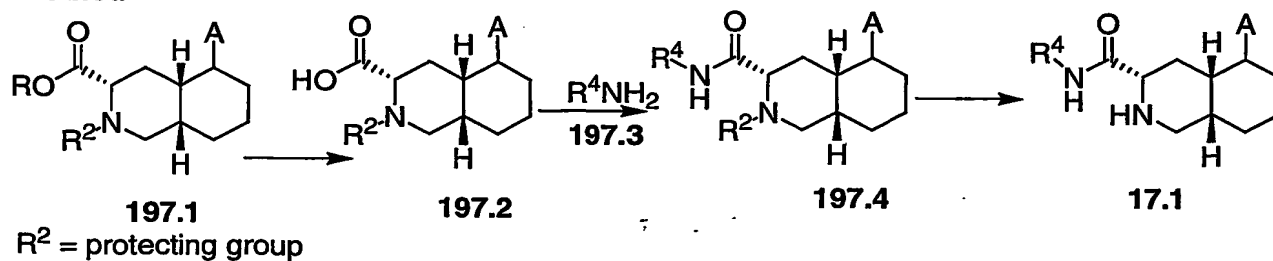
Scheme 196
Method



Example

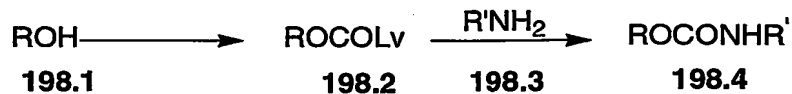


Scheme 197
Method

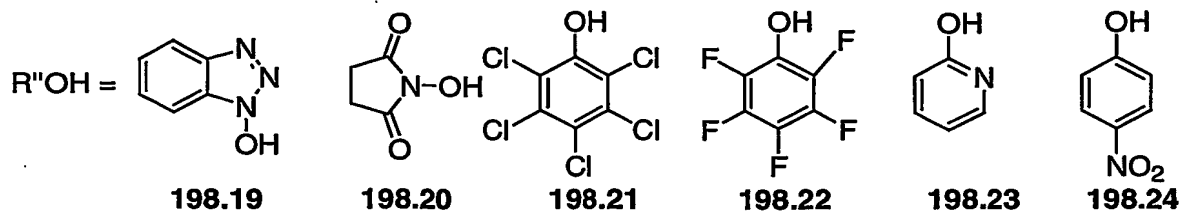
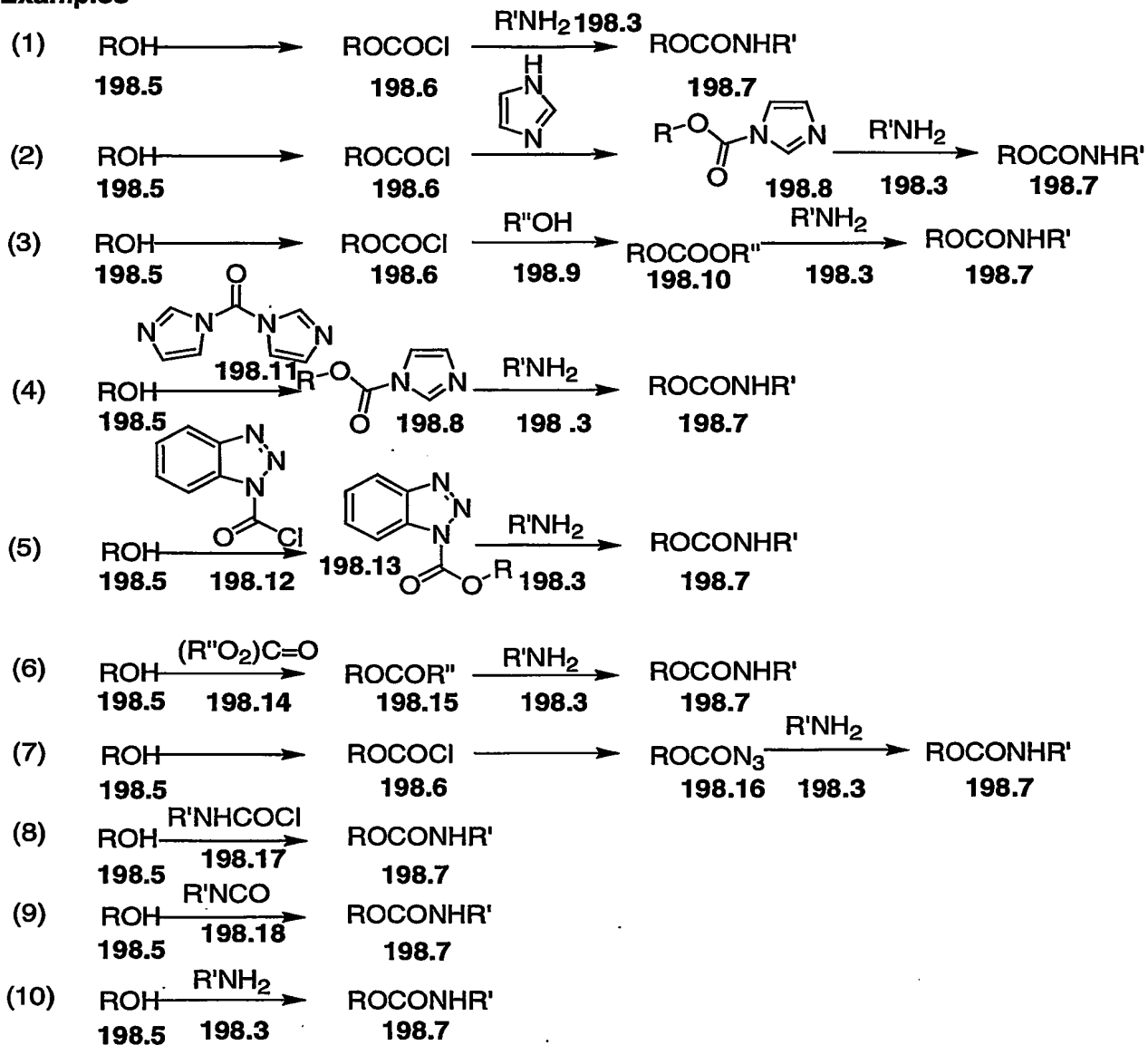


Scheme 198

General reaction



Examples



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 197 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to the phosphonate esters 1 - 24, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 199. The group R in Scheme 199 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1 - 24 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1 - 24. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 199.1 into the corresponding phosphonate monoester 199.2 (Scheme 199, Reaction 1) is accomplished by a number of methods. For example, the ester 199.1 in which R¹ is an aralkyl group such as benzyl, is converted into the monoester compound 199.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 199.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 199.2 is effected by treatment of the ester 199.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 199.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters 199.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, are converted into the monoester 199.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **199.1** or a phosphonate monoester **199.2** into the corresponding phosphonic acid **199.3** (Scheme **199**, Reactions **2** and **3**) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **199.2** in which R¹ is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **199.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **199.2** in which R¹ is alkenyl such as, for example, allyl, is converted into the phosphonic acid **199.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

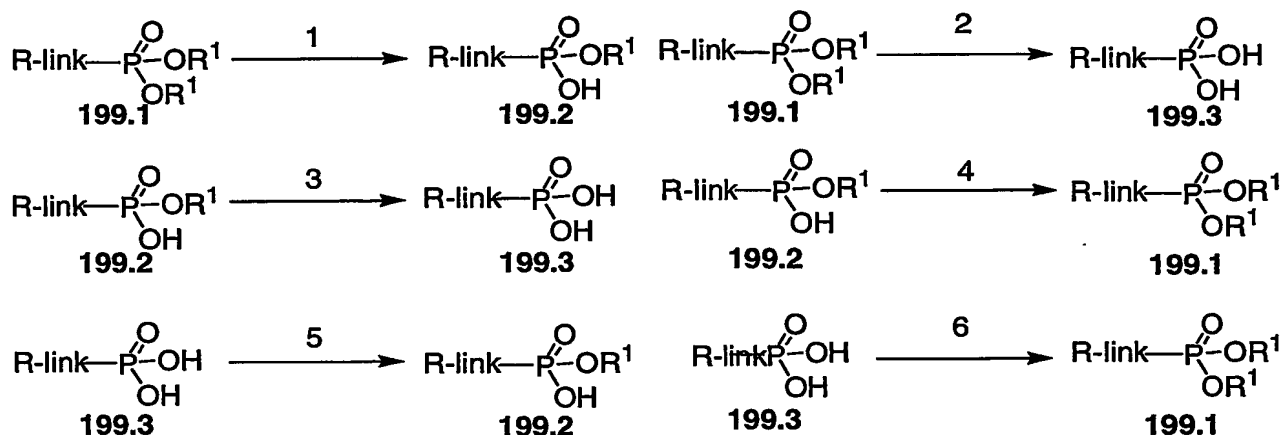
The conversion of a phosphonate monoester **199.2** into a phosphonate diester **199.1** (Scheme **199**, Reaction **4**) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **199.2** is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **199.2** to the diester **199.1** is effected by the use of the Mitsunobu reaction, as described above (Scheme **142**). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **199.2** is transformed into the phosphonate diester **199.1**, in which the

introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **199.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **199.1**.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **199**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ **199.3** is transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1** (Scheme **199**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **199.1**.

Scheme 199

General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes 133 - 192)

- 5 are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into indanols (Schemes 133 - 137) are applicable to the introduction of phosphonate moieties into phenylpropionic acids, thiophenols, tert. butylamines, pyridines, benzyl halides, ethanolamines, aminochromans, phenylalanines and benzyl alcohols, and the methods
- 10 described for the introduction of phosphonate moieties into the above-named substrates (Schemes 138 - 192) are applicable to the introduction of phosphonate moieties into indanol substrates.

Preparation of phosphonate intermediates 23 and 24 with phosphonate moieties

- 15 incorporated into the R^2 , R^3 , R^5 , R^{10} or R^{11} groups.

The chemical transformations described in Schemes 1 - 192 illustrate the preparation of

- compounds 1 - 22 in which the phosphonate ester moiety is attached to the indanol moiety, (Schemes 1 - 4, 76 - 84), the phenyl group (Schemes 5 - 8, 21 - 24, 37 - 40, 49 - 52, 58 -
- 20 61, 67 - 68, 74, 75, 101 - 108, 125 - 132) the tert. butylamine group, (Schemes 9 - 12, 25 - 28, 41 - 44, 109 - 116), the pyridine group (Schemes 13 - 16), the decahydroisoquinoline group (Schemes 17 - 20, 45 - 48, 117 - 124), the ethanolamine group (Schemes 29- 32, 93 - 100), the aminochroman group (Schemes 33 - 36, 85 - 92), and the thiophenyl group

(Schemes 53 – 57, 62 – 66, 69 – 73). The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$. The resultant phosphonate-containing analogs, designated as $R^{2a}R^{3a}NH$, $R^{5a}SH$, $R^{5a}CH_2I$, $R^{10a}CO$, $R^{11a}SH$, and $R^{11a}CH_2CH(NH_2)COOH$ are then, using the procedures described above, employed in the preparation of the compounds 23 and 24. The procedures required for the utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$. For example, Schemes 200-204 and Schemes 205-207 depict the introduction of the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, $[OH]$, $[NH_2]$, $[SH]$ onto the R^2R^3NH amines A10a and A10b in Chart 4, to give amines 200.5 and 205.10 respectively. These amine products are then utilized in the generation of compounds 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ in Chart 3 following the same procedures outlined in Schemes 13 and 15 but replacing the amine 13.1 with 200.5 or 205.10 respectively.

Preparation of piperazine furan compounds 200.5 with phosphonate attachments

Schemes 200 - 204 depict the preparation of the piperazine furan aryl phosphonate compounds 200.5 that are employed in the preparation of the phosphonate esters 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ as described above.

Scheme 200 depicts the preparation of piperazine biaryl phosphonates in which the terminal aryl ring bears the phosphonate moiety through a linking group. Methods for the preparation of the reagents 200.2 are shown in Schemes 201-204. Furan 200.1 prepared as described in WO02/096359, is treated with the aryl bromide 200.2 in the presence of palladium catalyst by the method of Gronowitz et al. (J. Heterocyclic Chemistry, 1995, 35, p. 771) to give 200.3. The product 200.3 is then subjected to the sequence of reactions and conditions described in WO02/096359 to prepare the piperazine 200.5. The preparation of reagent 200.6 where $R^4 = CH_2CF_3$ is also described in WO02/096359. Alternatively, deprotection of amines 164.1 by treatment with trifluoroacetic acid at room temperature as described in Int. J. Pept. Protein Res., 12, 258, 1978, followed by treatment with alloc chloro formate and a base such as

pyridine, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 526-527 yields **200.6** where R^4 is as defined in Chart 1.

Scheme **201** depicts the preparation of phosphonates **200.2** in which the phosphonate moiety is attached to the phenyl ring by means of a heteroatom and an alkyl chain. Many halogenated aromatic compounds are commercially available or can be generated from readily available aromatic compounds through aromatic substitution. Methods for chlorinating or brominating an aryl ring can be found in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999 p619. The phenol, thiol or amine **201.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **201.2**. For example, the phenols **201.5** (Aldrich) or **201.9** (Apollo-Chem) are reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether products. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the products **201.6** and **201.10** respectively. Alternatively treatment of amine **201.11** (Apollo) or **201.7** (Aldrich) with the dialkyl trifluoromethylsulfonyloxymethyl phosphonate **140.6** in the presence of a base as described above affords **201.12** and **201.8** respectively.

Using the above procedures, but employing, in place of the phenols and amines, different phenols, thiols or amines **201.1**, and /or different dialkyl trifluoromethyl-sulfonyloxymethyl phosphonates **140.2**, the corresponding products **201.2** are obtained.

Scheme **202** illustrates the preparation of compounds in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde **202.1** is reacted, under reductive amination conditions, as described in Scheme **135**, with a dialkyl aminoalkyl phosphonate **202.2**, to give the amine **202.3**.

For example, the aldehyde **202.4** (Aldrich) is reacted in ethanol with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and sodium triacetoxyborohydride, to produce the amine **202.5**.

Using the above procedures, but employing, in place of the aldehyde, **202.4** different aldehydes **202.1** and different phosphonates **202.2**, the corresponding products **202.3** are obtained.

5 Scheme **203** illustrates the preparation of aryl halides incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted aryl halide **203.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **202.2** to prepare the amide **203.2**.

For example, 2-chloro-4-bromobenzoic acid **203.4**, the preparation of which is described in
10 Bioorg. Med. Chem. Lett. 2001, 11, 10, p. 1257, is coupled in dimethylformamide solution, in the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide **203.5**.
Using the above procedures, but employing, in place of the benzoic acid **203.4**, different benzoic acids **203.1**, and/or different aminoalkyl phosphonates **202.2**, the corresponding
15 products **203.2** are obtained.

Scheme **204** illustrates the preparation of phosphonate-substituted aryl halides in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a benzoic acid **203.1** is first methylated to give methyl ester **204.1** and then reduced with a reducing
20 agent, as described in J. Org. Chem. 1987, 52, p. 5419 to give alcohol **204.2**. The alcohol **204.2** is then reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide **204.3**. The bromide **204.3** is reacted with a sodium dialkyl phosphite **204.5** or a trialkyl phosphite, to give the product **204.4**.

For example, acid **204.6** (Lancaster) is converted to the methyl ester **204.7** by refluxing in
25 methanol and concentrated sulfuric acid and then reduced with lithium aluminum hydride in THF to give **204.8** as described above. The product **204.8** is reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide **204.9**. This material is reacted with a sodium dialkyl phosphite **204.5**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **204.10**. Alternatively, the bromomethyl
30 compound **204.9** is converted into the phosphonate **204.10** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure,

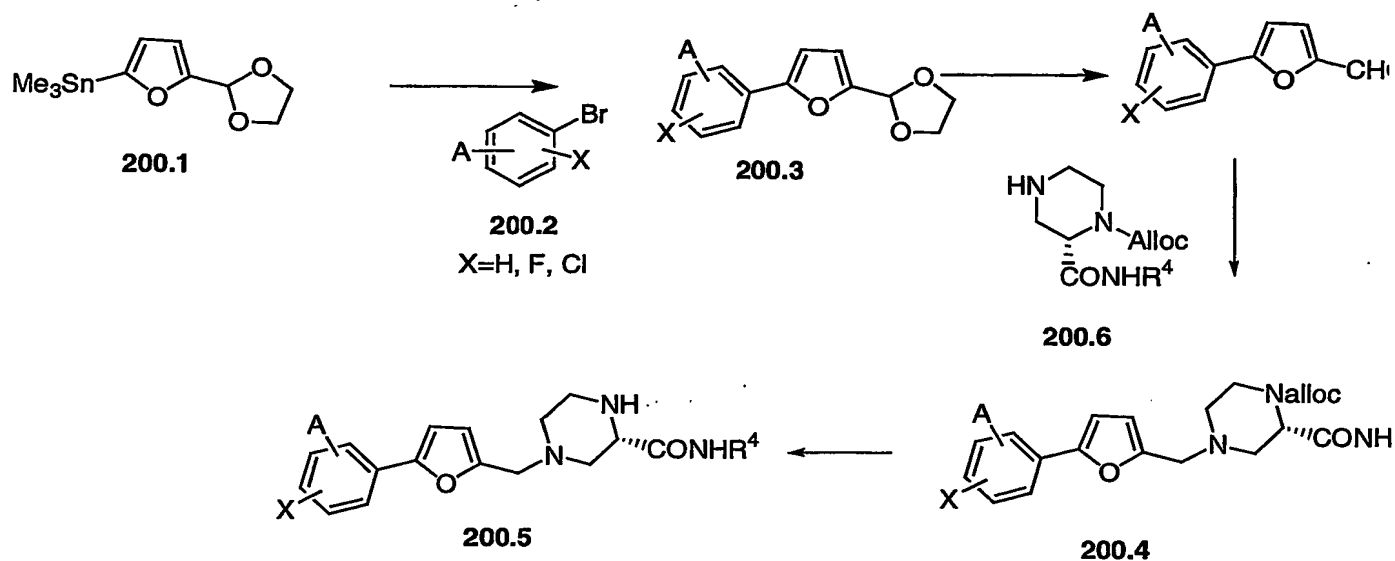
the bromomethyl compound **204.9** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate **204.10**.

Using the above procedures, but employing, in place of the acid **204.6**, different acids **203.1**, and different phosphites **204.5** there are obtained the corresponding aryl halides **204.4**.

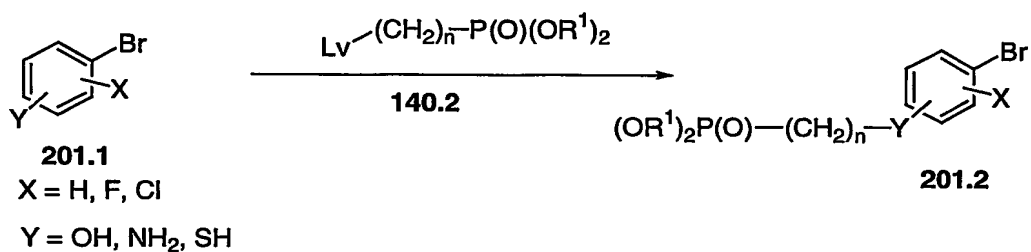
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The phosphonate-containing bromobenzene derivatives prepared as described in Schemes **201** - **204** are then transformed, as described in Scheme **200**, into the phenylfuran piperazine derivatives **200.5**.

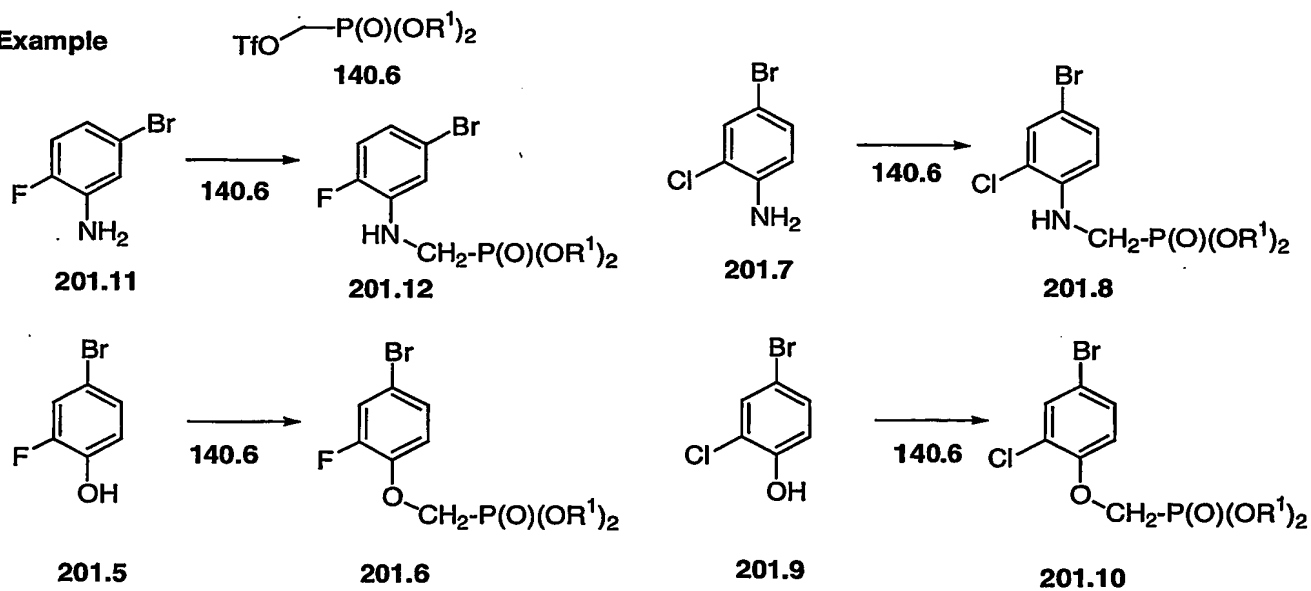
Scheme 200



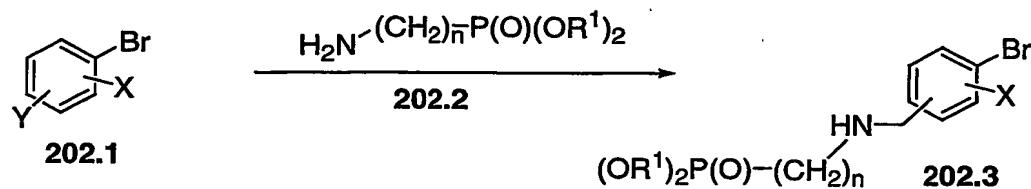
Scheme 201



Example



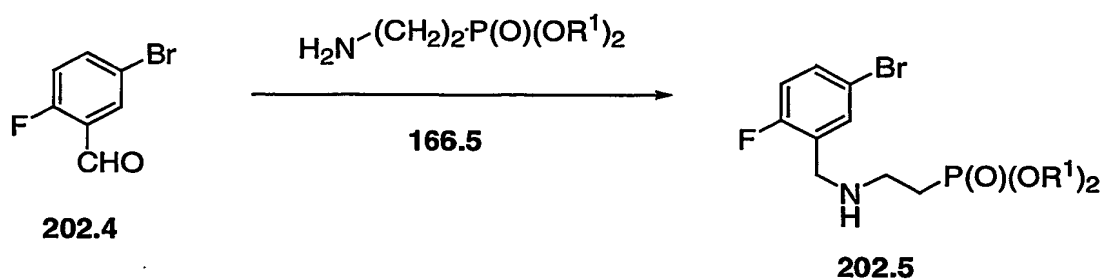
Scheme 202



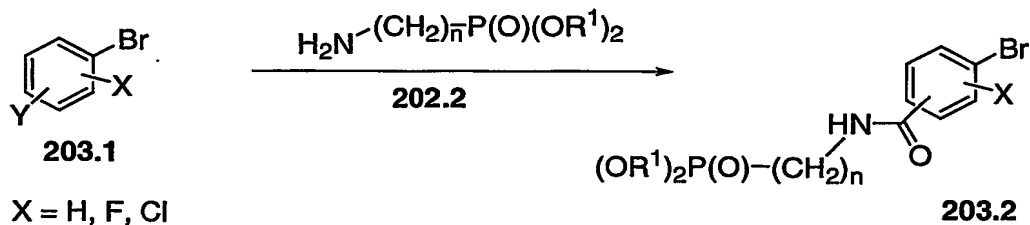
X = H, F, Cl

Y = CHO

Example



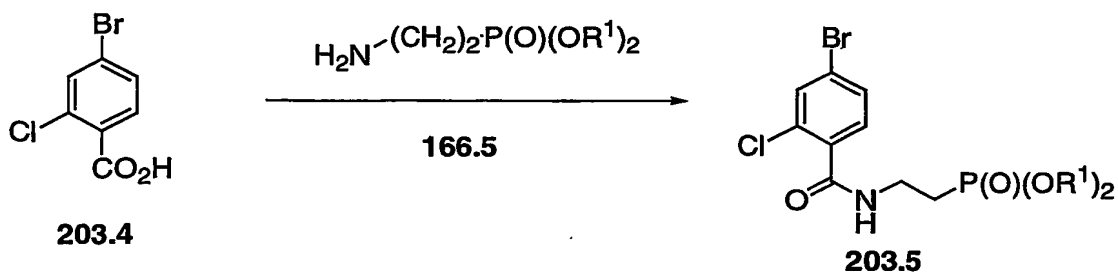
Scheme 203

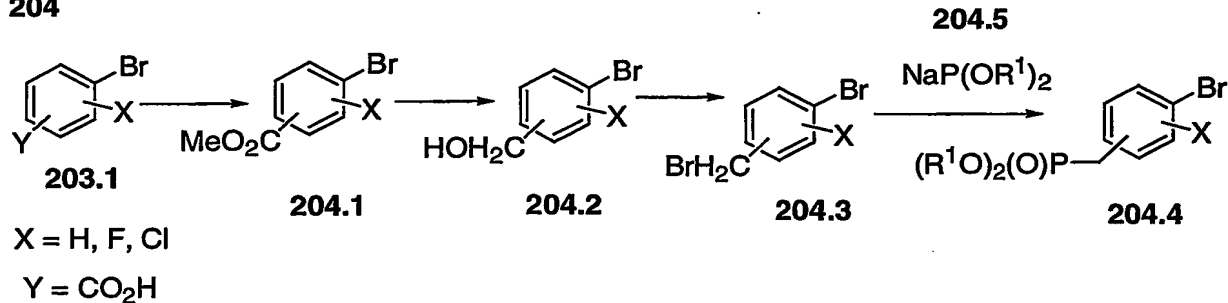
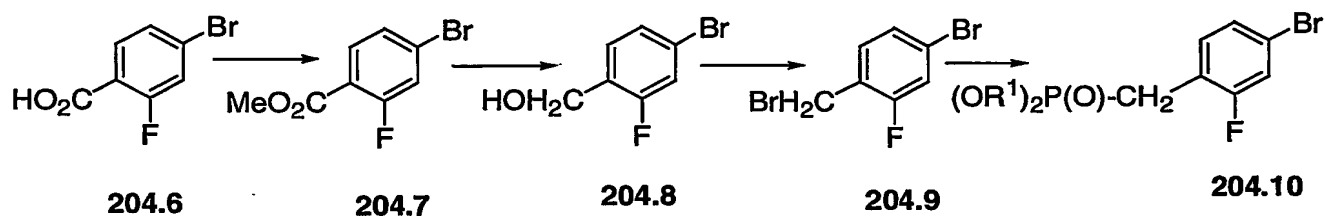


X = H, F, Cl

Y = CO₂H

Example



Scheme 204**Example**

Preparation of piperazine oxazole compounds 205.10 bearing phosphonate attachments

- 5 Schemes 205 - 207 depict the preparation of the piperazine oxazole phosphonate compounds 205.10 that are employed in the preparation of the phosphonate esters 23 where $\text{R}^2\text{R}^3\text{NH}$ is now $\text{R}^{2a}\text{R}^{3a}\text{NH}$ as described above.

- 10 Scheme 205 depicts the preparation of piperazine oxazole phosphonates 205.10 in which the terminal aryl ring bears the phosphonate moiety. The acid 205.1 is converted to the Weinreb amide, for example, as described in J. Med. Chem., 1994, 37, 2918, and then reacted with a methyl Grignard reagent e.g. MeMgBr. Examples of this procedure are reviewed in Org prep Proc Intl 1993, 25, 15. Ketone 205.3 is then brominated using conditions described in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 710-711.
- 15 For example, treatment of 205.3 with bromine in acetic acid yields 205.4. Conversion of the bromomethyl compound 205.4 into the piperazine derivative 205.10, via the intermediates 205.5 - 205.9, is effected by means of the reactions and procedures described in WO02/096359 for related compounds in which R^4 is CH_2CF_3 and A is H.

Scheme 206 illustrates the preparation of benzoic acid phosphonates in which the phosphonate moiety is attached by means of alkylene chains and a heteroatom O, S or N. In this procedure, a benzoic acid 206.1 is protected with a suitable protecting group (see Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch5 and then
5 reacted with a an equimolar amount of a dialkyl phosphonate 206.3, in which Ha is a leaving group e.g. halogen, to afford the alkyl phosphonate product 206.4. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 206.2. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is
10 employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed. Following this reaction the product 206.4 is hydrolyzed by treatment with base to give the acid 206.5

For example, benzoic acid 206.6, (Aldrich) is reacted with diazomethane in ether at 0°C to give the methyl ester 206.7 or simply refluxed in acidic methanol. The ester in acetonitrile at
15 60°C is treated with one molar equivalent of a dialkyl iodomethyl phosphonate 206.8, (Lancaster) to give the ether product 206.9. This product 206.9 is then hydrolyzed by treatment with lithium hydroxide in aqueous THF to give the acid 206.10.

Using the above procedures, but employing, in place of the benzoic acid 206.6, different acids 206.1, and/or different haloalkyl phosphonates 206.3, the corresponding products 206.5 are
20 obtained.

Scheme 207 depicts the preparation of phosphonate esters linked to a benzoic acid nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 207.3 is
25 coupled with an aromatic bromo compound 207.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
30 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 207.4. Deprotection, or hydrogenation of the double bond

followed by deprotection, affords respectively the unsaturated phosphonate acid **207.5**, or the saturated analog **207.6** respectively.

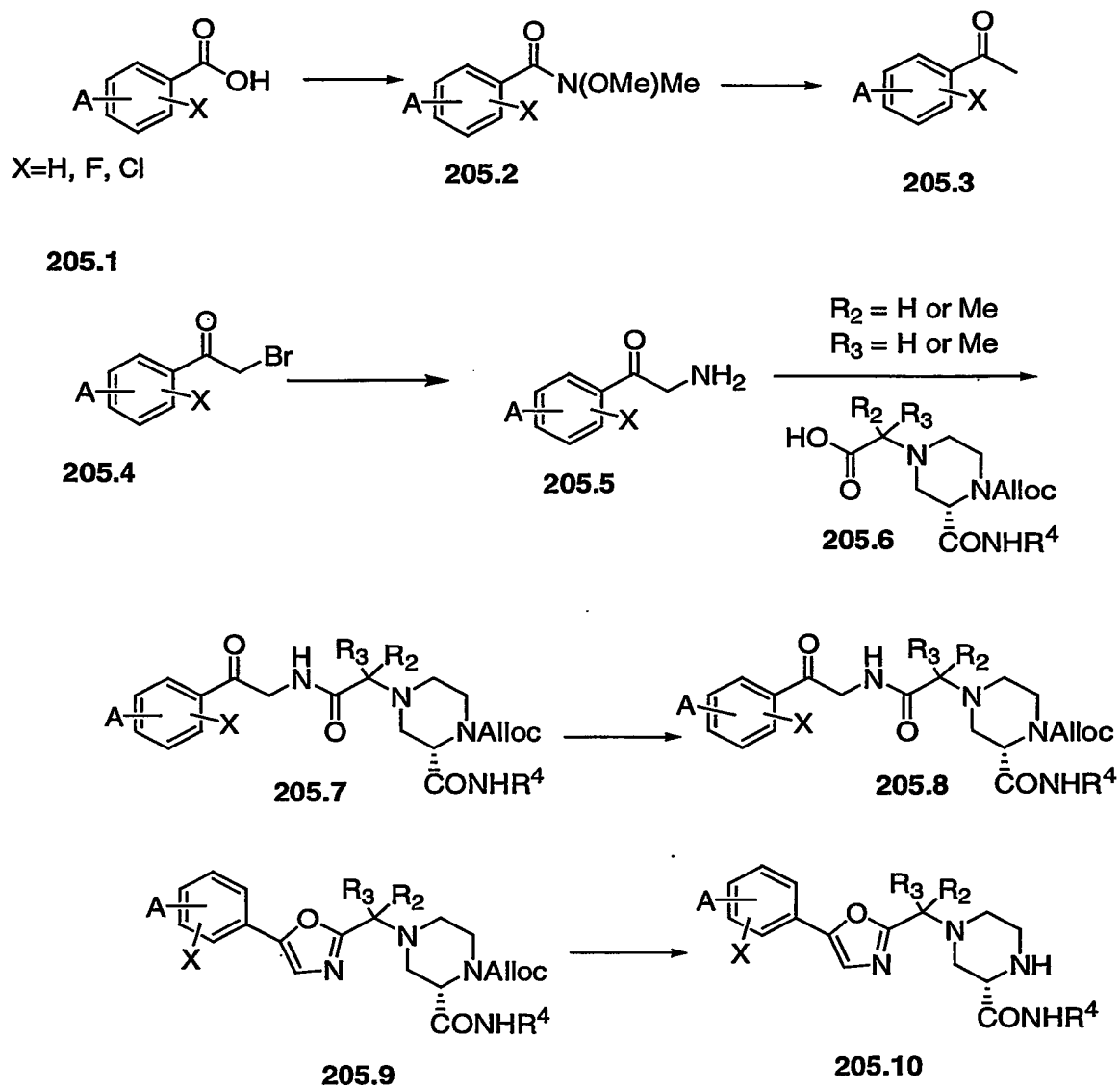
For example, 4-bromo-3-fluorobenzoic acid **207.7** (Apollo) is converted to the tert butyl ester **207.8** by treatment with t-butanol and DCC in the presence of dimethylaminopyridine. The

5 ester **207.8** is then reacted with a dialkyl 1-propenyl phosphonate **150.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the
10 coupled product **207.10**. Deprotection as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 406-408, then affords the acid **207.11**. Optionally, the acid **207.11** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme **138**, to yield the saturated product **207.12**.

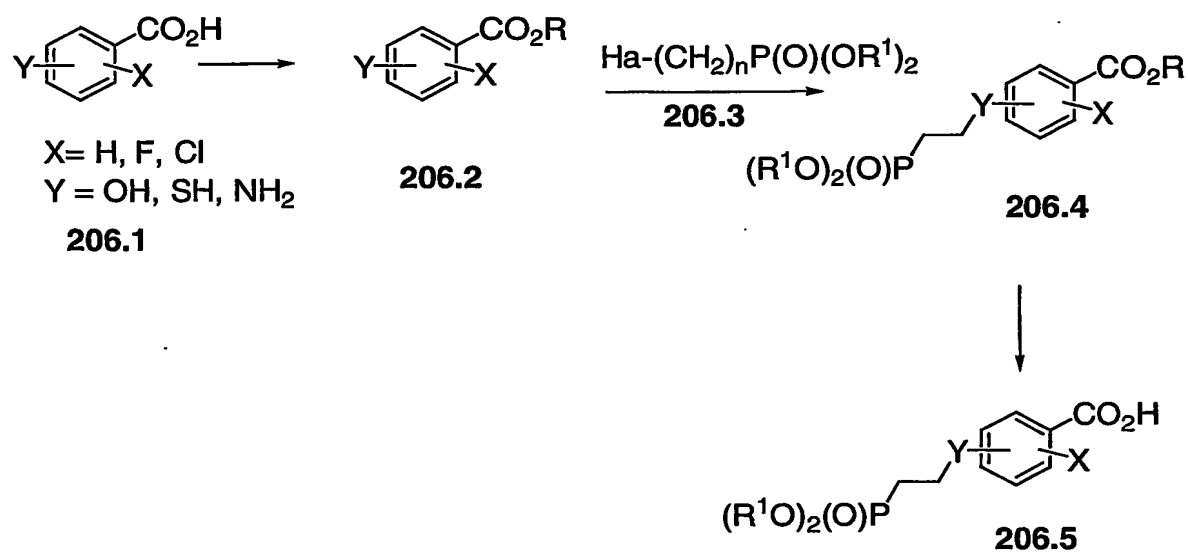
15 Using the above procedures, but employing, in place of the acid compound **207.7**, different acid compounds **207.1**, and/or different phosphonates **207.3**, there are obtained the corresponding products **207.5** and **207.6**.

The phosphonate-containing benzoic acids, prepared as described in Schemes **206** and **207**,
20 are then transformed, using the procedures shown in Scheme **205**, into the phenyloxazole piperazine derivatives **205.10**.

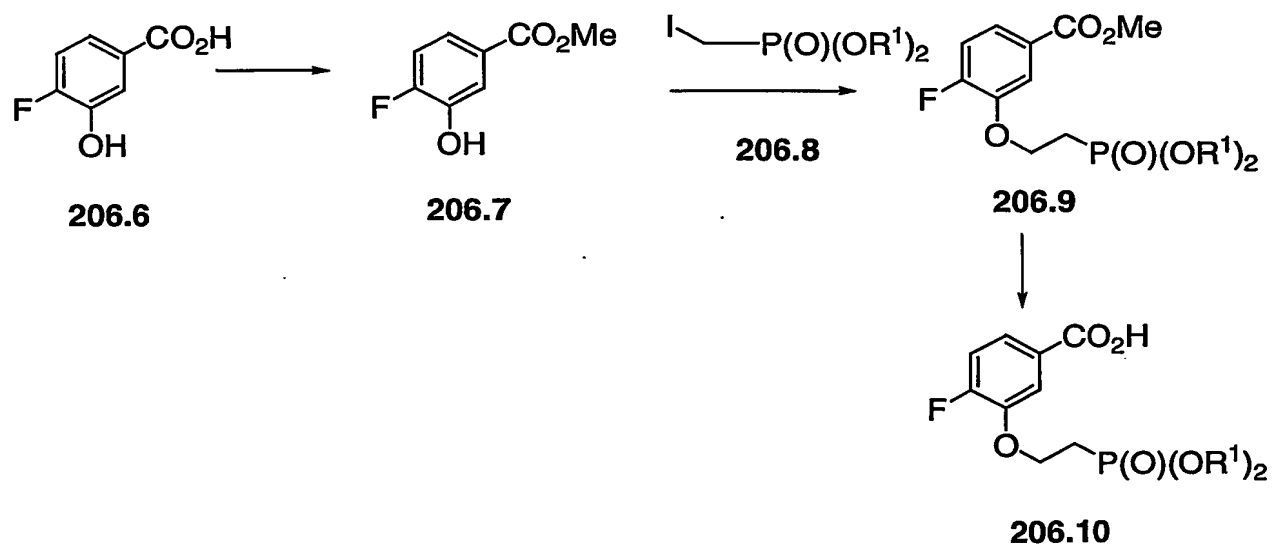
Scheme 205



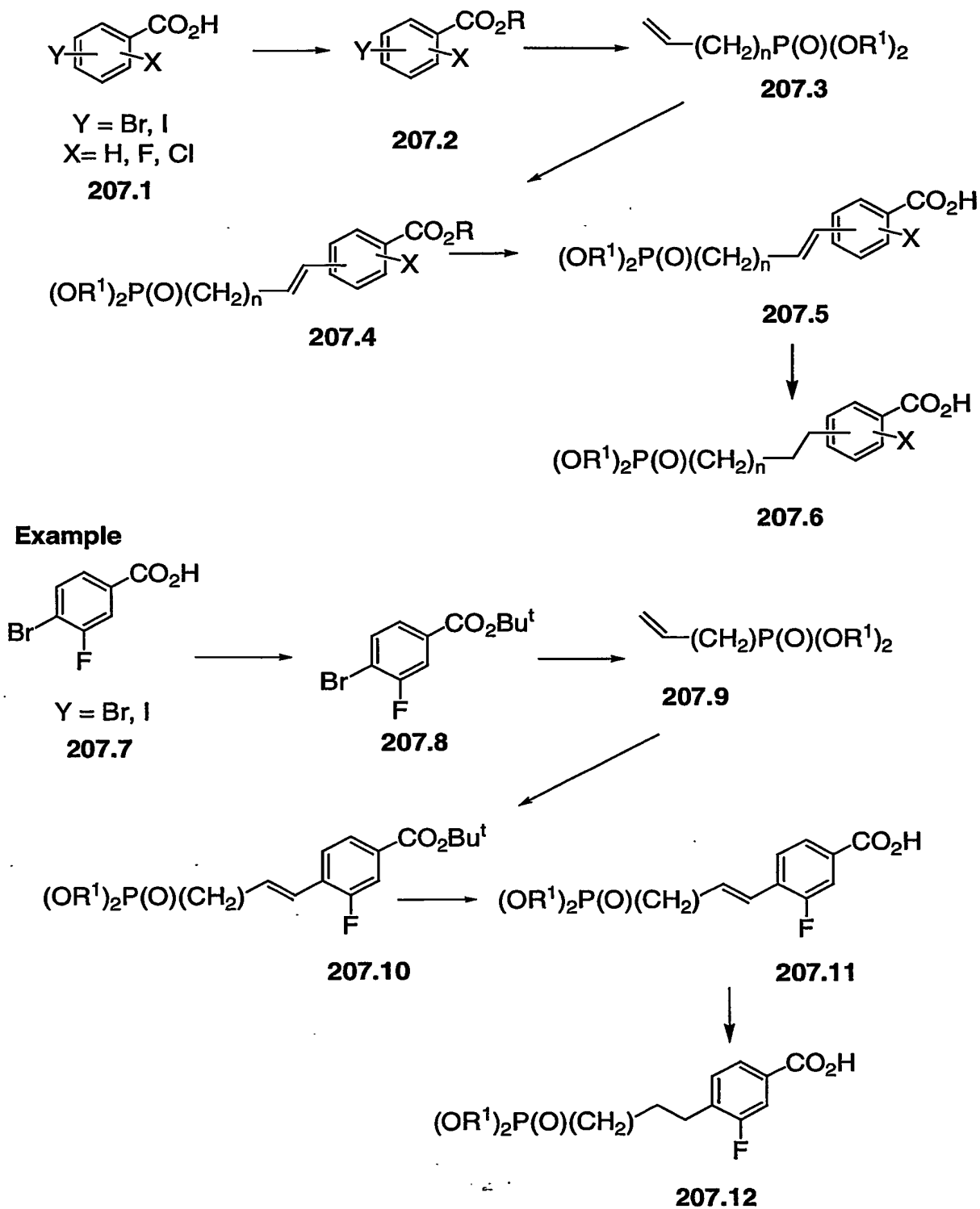
Scheme 206



Example

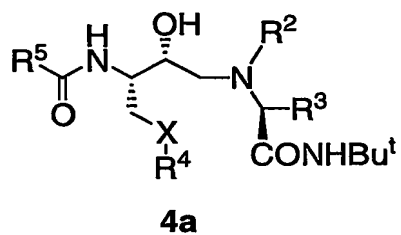
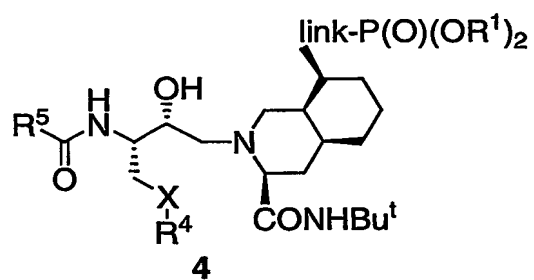
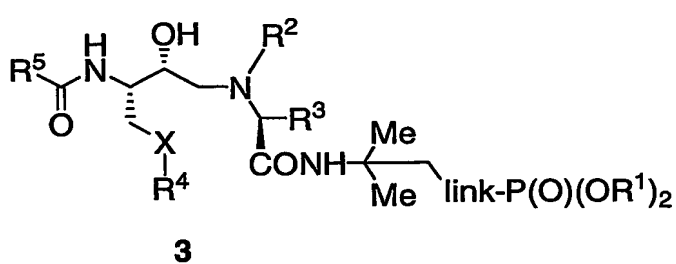
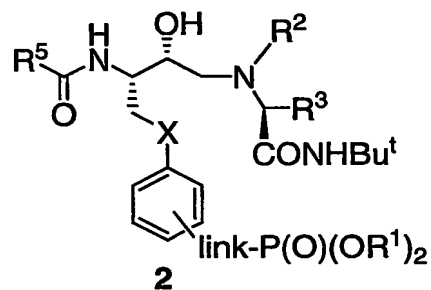
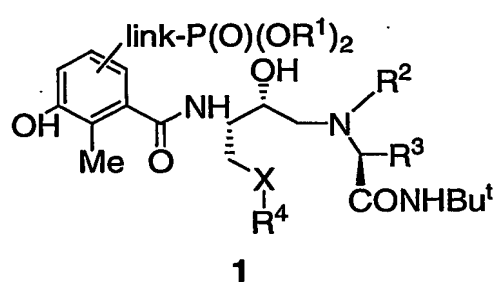


Scheme 207



Nelfinavir-like phosphonate protease inhibitors - (NLPPD)**Preparation of the intermediate phosphonate esters.**

- 5 The intermediate phosphonate esters **1** to **4a** of this invention are shown in Chart **1**. Subsequent chemical modifications, as described herein, permit the synthesis of the final compounds of this invention.
- The structures of the amine components $R^2NHCH(R^3)CONHBut$ **6-20e** are shown in Chart **2**. Although specific stereoisomers of some of the amines are shown, all stereoisomers of the
- 10 amine components are utilized. Chart **2** also illustrates that, in addition to the tert. butyl amines **5**, the corresponding 2,2,2-trifluoroethyl and 2-methylbenzyl amides are utilized in the synthesis of the phosphonate intermediate compounds of this invention.
- Chart **3** depicts the structures of the R^4 components **21-26**. Charts **4a-4c** illustrate the structures of the carboxylic acid components R^5COOH , **C1-C49**.
- 15 The intermediate compounds **1** to **4a** incorporate a phosphonate moiety connected to the a nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **5** and **5a** illustrate examples of the linking groups **38-59** present in the structures **1-4a**, and in which "etc" refers to the scaffold, e.g., nelfinavir.
- Schemes **1 - 50** illustrate the syntheses of the intermediate phosphonate compounds of this
- 20 invention, **1-4a**, and of the intermediate compounds necessary for their synthesis.

Chart 1. Structures of phosphonate ester intermediate compounds

$R^1 = \text{H, alkyl, alkenyl, aryl, aralkyl}$

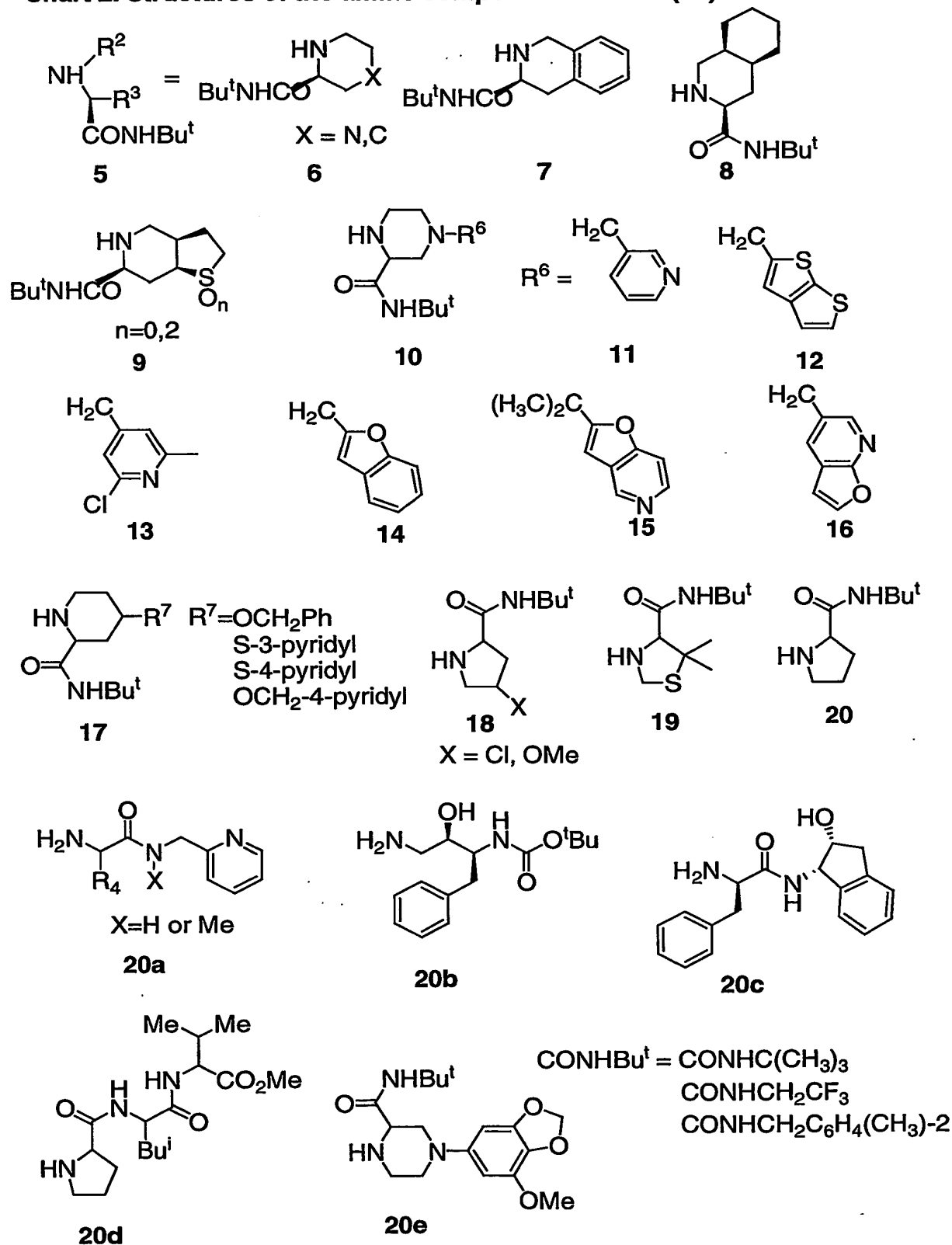
Chart 2. Structures of the amine component $R^2NHCH(R^3)CONHBu^t$ 

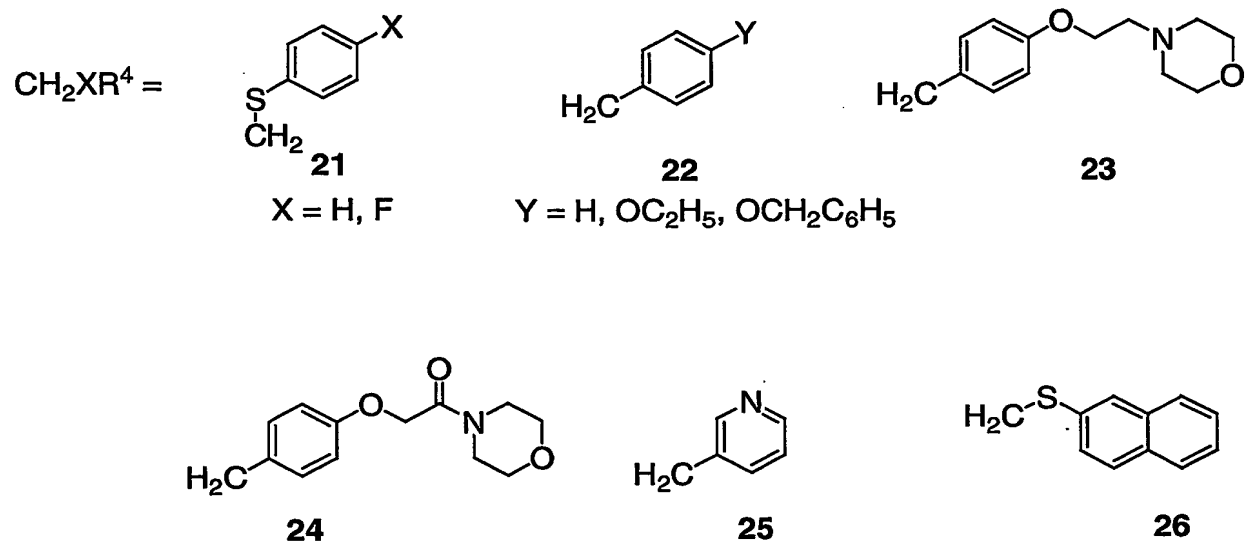
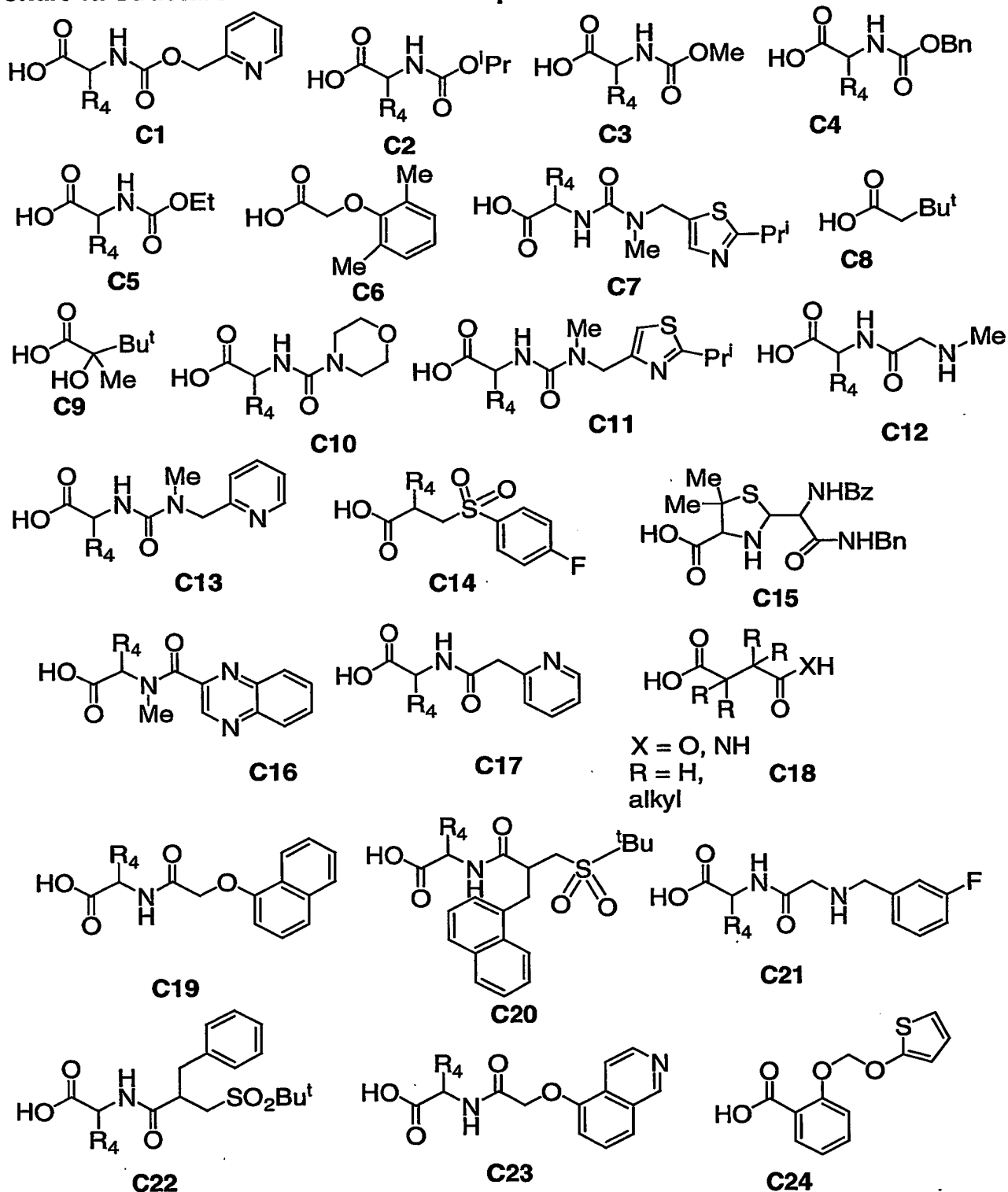
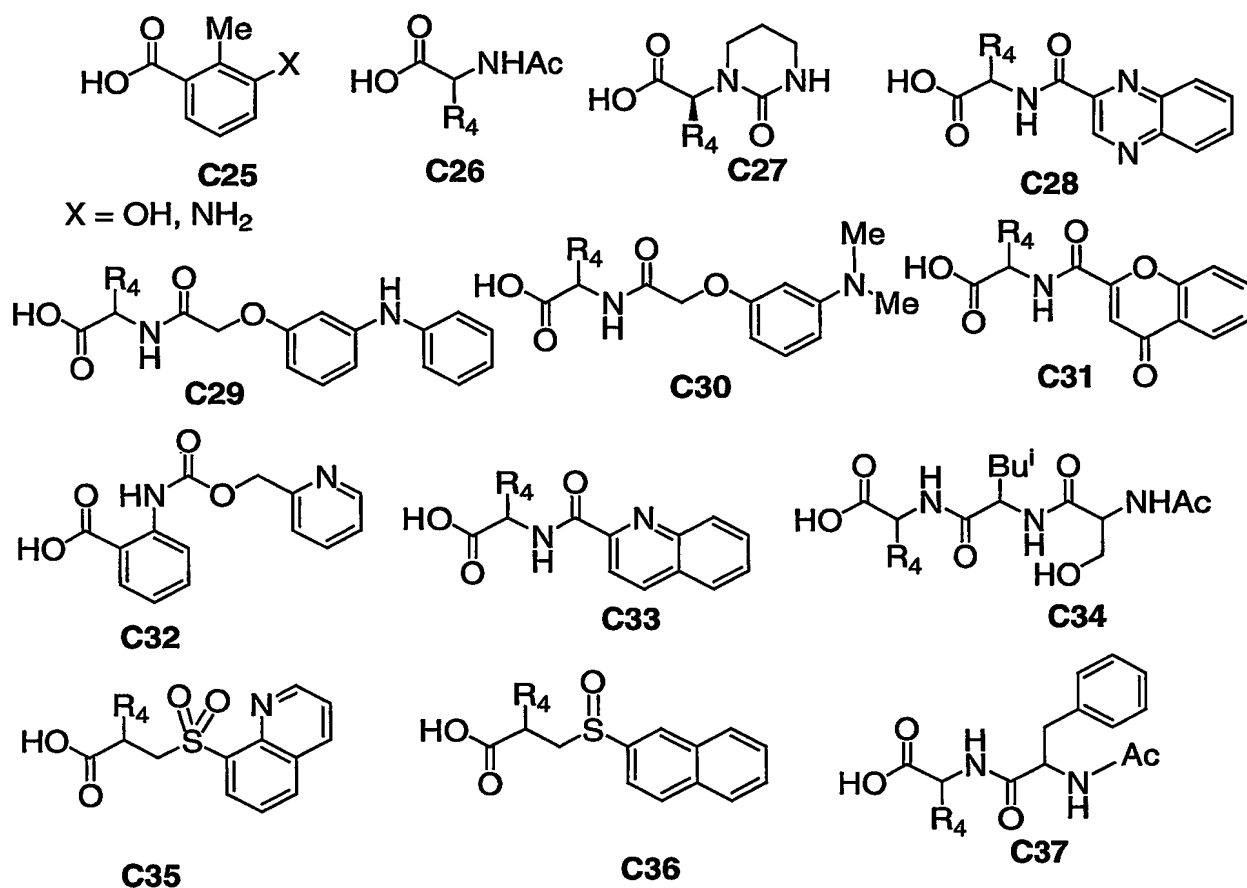
Chart 3. Structures of the R⁴ components

Chart 4a Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 4b Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

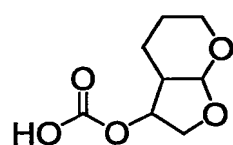
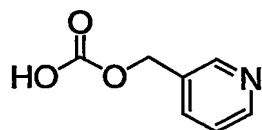
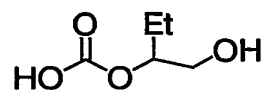
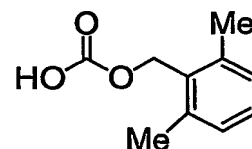
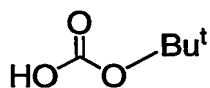
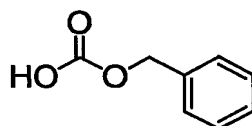
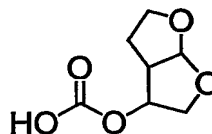
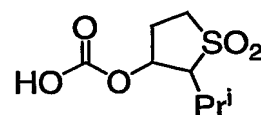
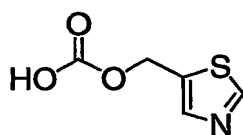
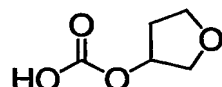
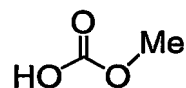
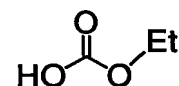
Chart 4c Structures of the R⁵COOH components**C38****C39****C40****C41****C42****C43****C44****C45****C46****C47****C48****C49**

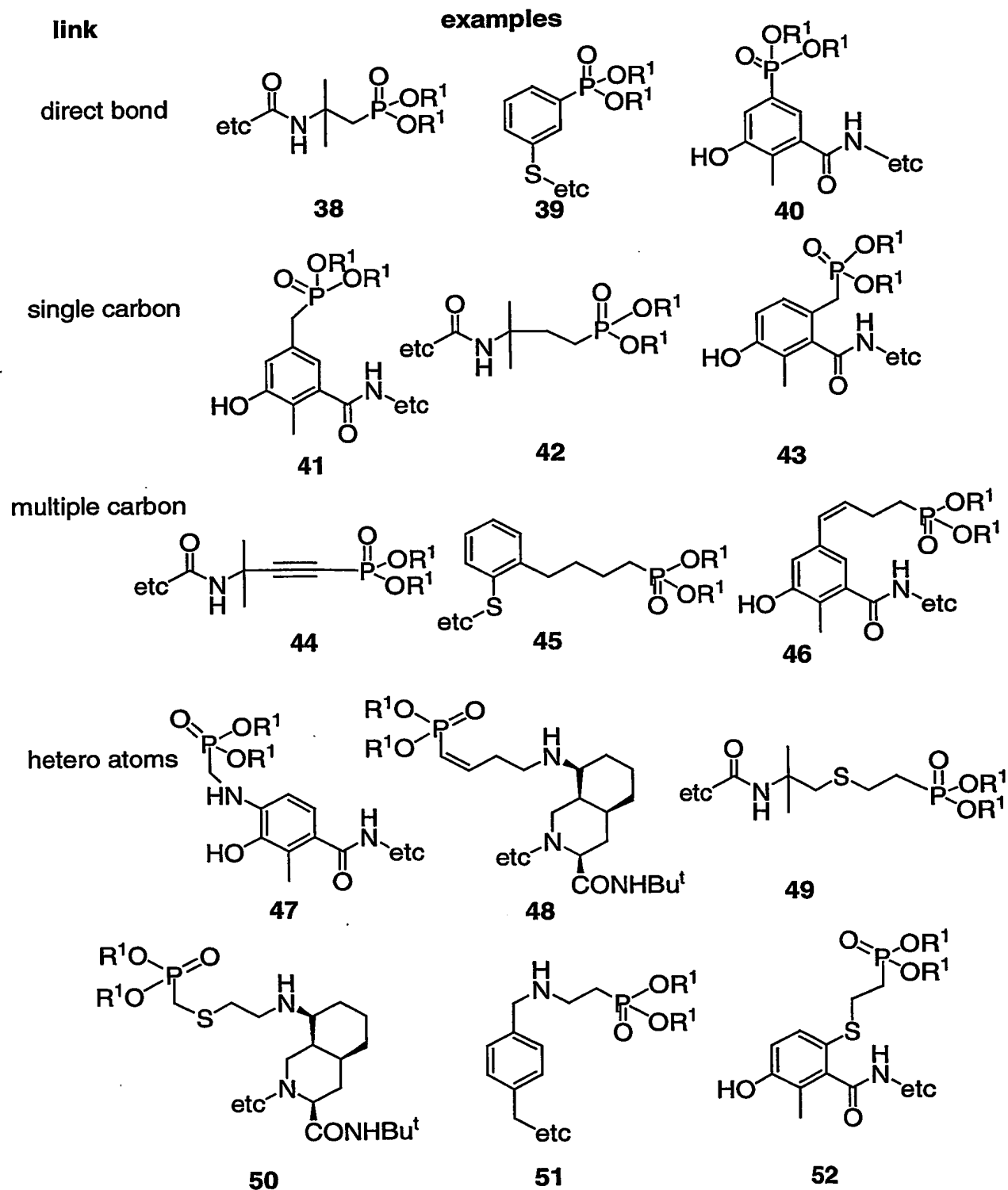
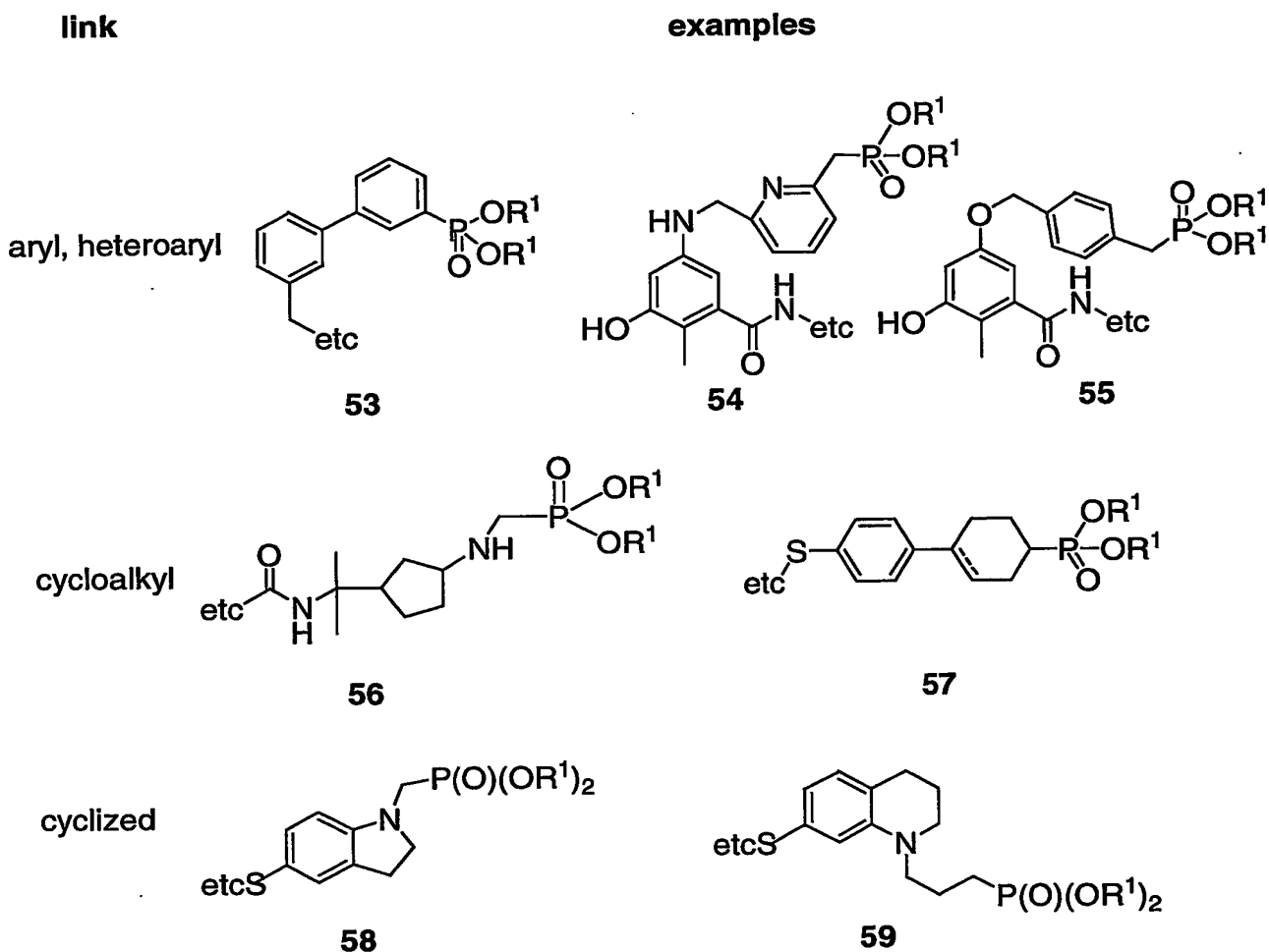
Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

Chart 5a Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

5 Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective

10 Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1, in which X=S.

The syntheses of the phosphonates 1 in which X=S, and in which the group link-P(O)(OR¹)₂ is attached to the benzoic acid moiety, are shown in Schemes 1- 3.

5 Scheme 1 illustrates the preparation of the phosphonate intermediate compounds 1, or precursors thereto. 4-Amino-tetrahydro-furan-3-ol 60, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with the carboxylic acid 61, or an activated derivative thereof, the preparations of which are described below, to form the amide 62.

10 The preparation of amides by reaction of carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

15 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

20 Preferably, the carboxylic acid is first converted into the acid chloride by reaction with, for example, thionyl chloride, oxalyl chloride and the like. The acid chloride 61, in which X is Cl, is then reacted with an equimolar amount of the amine 60, in the presence of a weak inorganic base such as sodium bicarbonate, in an aprotic solvent such as dichloromethane, at ambient temperature, to afford the amide 62.

25 The hydroxyl group on the tetrahydrofuran moiety so obtained is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane.

Preferably, the hydroxy amide 62 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 63.

30 The product 63, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 64. The rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst.

Preferably, the mesylate **63** is dissolved in an acylating agent such as acetic anhydride at about 0°, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **64**.

5 The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine.

The compound **64** is reacted with an amine **5**, as defined in Chart 2, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **65**.

10 Preferably, the mesylate compound **64** is reacted with an equimolar amount of the amine **5**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **65**.

15 The isoxazoline compound **65** is then reacted with a thiol R⁴SH **66**, in which R⁴ is phenyl, 4-fluorophenyl or 2-naphthyl, as shown in Chart 3, to afford the thioether **1**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product **1**.

Preferably, the isoxazoline **65** is reacted, in methanol, with an equimolar amount of the thiol R⁴SH **66**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **1**.

20 Alternatively, the compounds **1** can be obtained by means of the reactions shown in Scheme 2. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **67**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R⁴SH **66**, as defined above, to afford the thioether **68**.

25 The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours, to afford **68**.

30 Preferably the mesylate **67** is reacted with an equimolar amount of the thiol R⁴SH **66**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, to give the product **68**.

The 1,3-dioxolane protecting group present in the compound **68** is removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **69**. Methods

for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990, p. 191. For example, the 1,3-dioxolane compound **68** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture.

5 Preferably, the 1,3-dioxolane **68** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the product **69**.

The primary hydroxyl group of the diol **69** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as
10 dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **69** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the ester **70**.

The hydroxy ester **70** is next reacted with a sulfonyl chloride such as methanesulfonyl chloride,
15 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **71**.

Preferably, equimolar amounts of the carbinol **70** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **71**.

The compound **71** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane
20 **72**.

The mesylate or analogous leaving group present in **71** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **72** with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester **71** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic
25 solvent.

Preferably, the mesylate **71** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **72**.

The oxirane compound **72** is then subjected to regiospecific ring-opening reaction by treatment with an amine **5**, to give the aminoalcohol **73**.

30 The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0° to 100°, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **73**.

Preferably, equimolar amounts of the reactants **5** and **72** are reacted in aqueous methanol at about 60° in the presence of potassium carbonate, for about 6 hours, to afford **73**.

The carbobenzyloxy (cbz) protecting group in the product **73** is removed to afford the free amine **74**. Methods for removal of cbz groups are described, for example, in Protective

5 Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Second Edition, p. 335.

The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **73** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **74**.

10 Preferably, the cbz group is removed by the reaction of **73** with potassium hydroxide in an alcohol such as isopropanol at ca. 60° to afford the amine **74**.

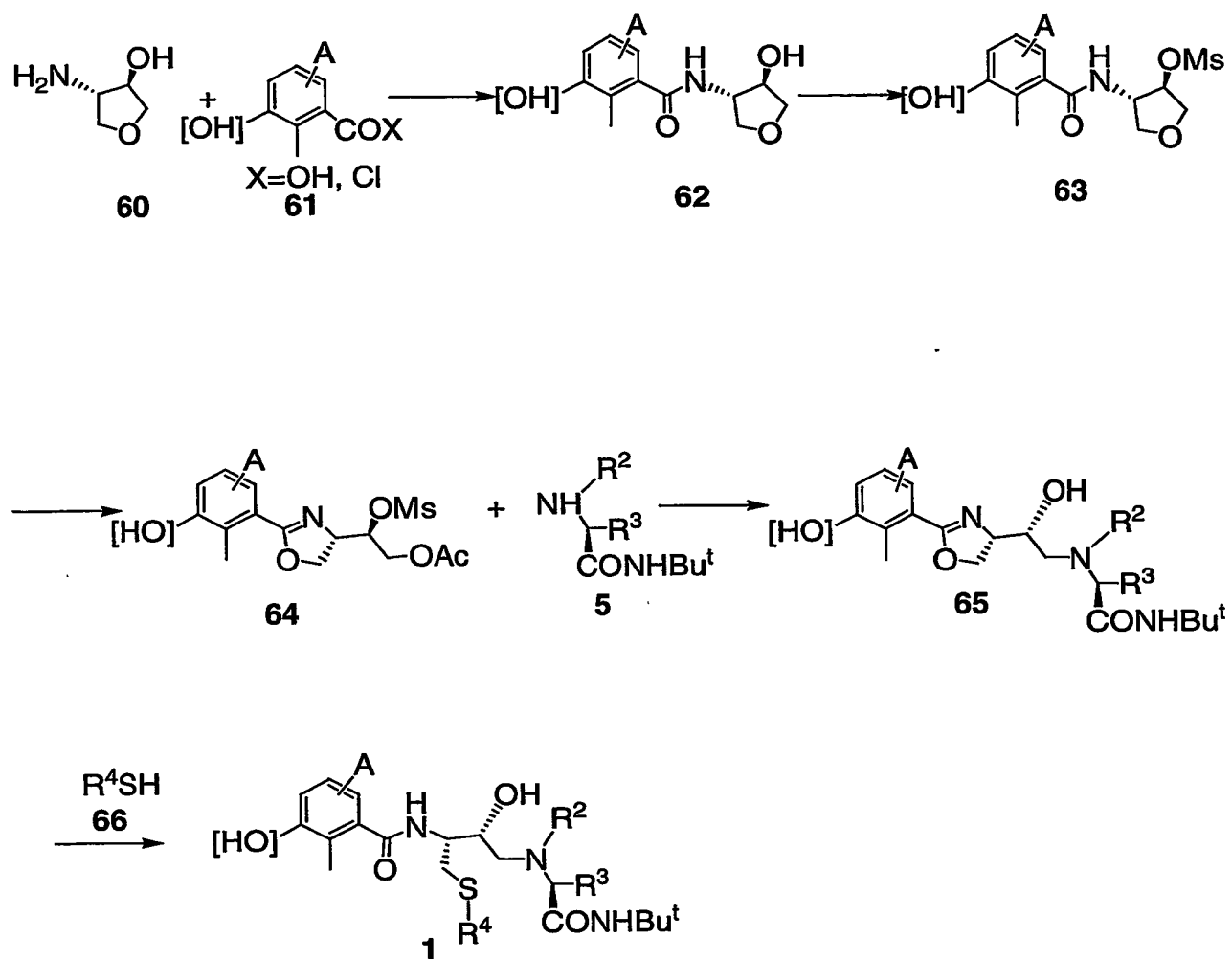
The amine **74** so obtained is next acylated with a carboxylic acid or activated derivative **61**, using the conditions described above for the conversion of **60** to **62**, to yield the final amide product **75**.

15 The reactions shown in the above-described Schemes 1 and 2 depict the preparation of intermediates **1** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 3 shows the conversion of the compounds **75** in which A is OH, SH, NH, to the compounds **1** in which A is link-P(O)(OR¹)₂.

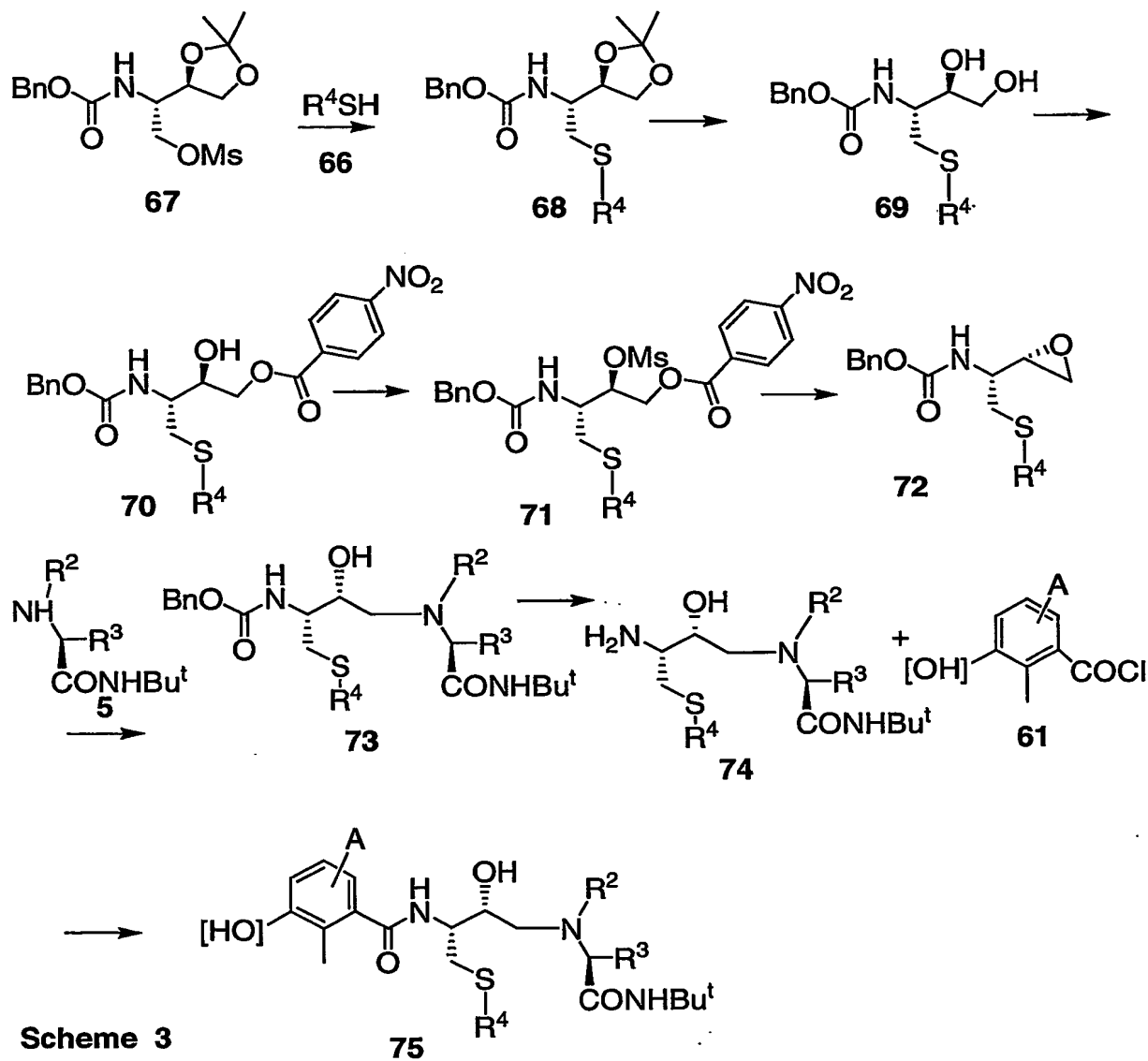
20 Methods for these transformations are described below, Schemes 20-48, in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 1

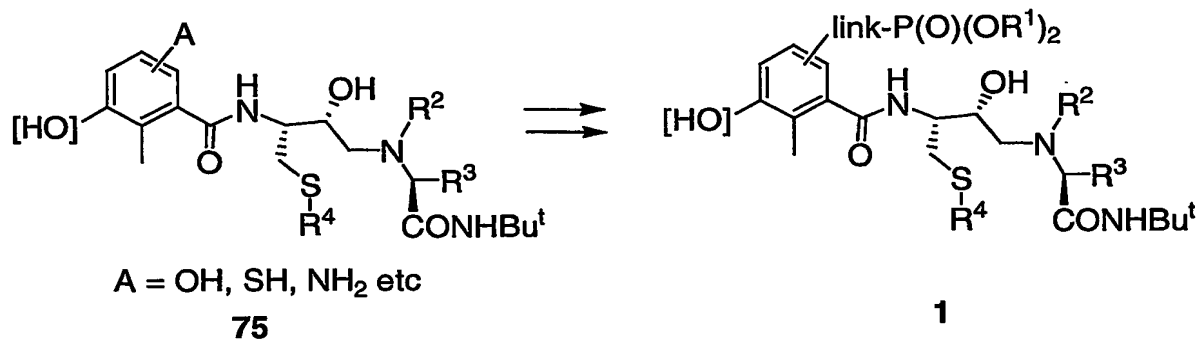


$\text{A} = \text{link}-(\text{P})(\text{OR}^1)_2$ or $\text{A} = \text{OH}, \text{SH}, \text{NH}, \text{etc}$

Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2, in which X = S.

The synthesis of the phosphonate compounds **2** in which the link-P(O)(OR¹)₂ group is attached to the phenylthio moiety, is shown in Scheme 4.

In this sequence, 4-amino-tetrahydro-furan-3-ol, **60**, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R⁵COX, **76**, using the conditions described above for the preparation of the amide **62**, Scheme 1, to afford the amide **77**. The compounds **77**, and analogous acylation products described below, in which the carboxylic acid R⁵COOH is one of the carbonic acid derivatives C36-C49, as defined in Chart 4c, are carbamates. Methods for the preparation of carbamates are described below, (Scheme 50).

- 10 The amide product **77** is then transformed, using the sequence of reactions shown in Scheme 4, into the isoxazoline compound **80**. The conditions for this sequence of transformations are the same as those described for the preparation of the isoxazoline **65** in Scheme 1.

- 15 The isoxazoline compound **80** is then reacted with a thiol compound **66**, in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether **81**.

The conditions for this reaction are the same as those described above for the preparation of the thioether **1**, (Scheme 1).

- 20 Alternatively, the thioether **81** can be prepared by the sequence of reactions shown in Scheme 5. In this sequence, the previously described 1,3-dioxolane mesylate compound **67** is reacted with a thiol compound **66** in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether **82**. The conditions for this reaction are the same as those described above for the preparation of the thioether **68**, (Scheme 2).

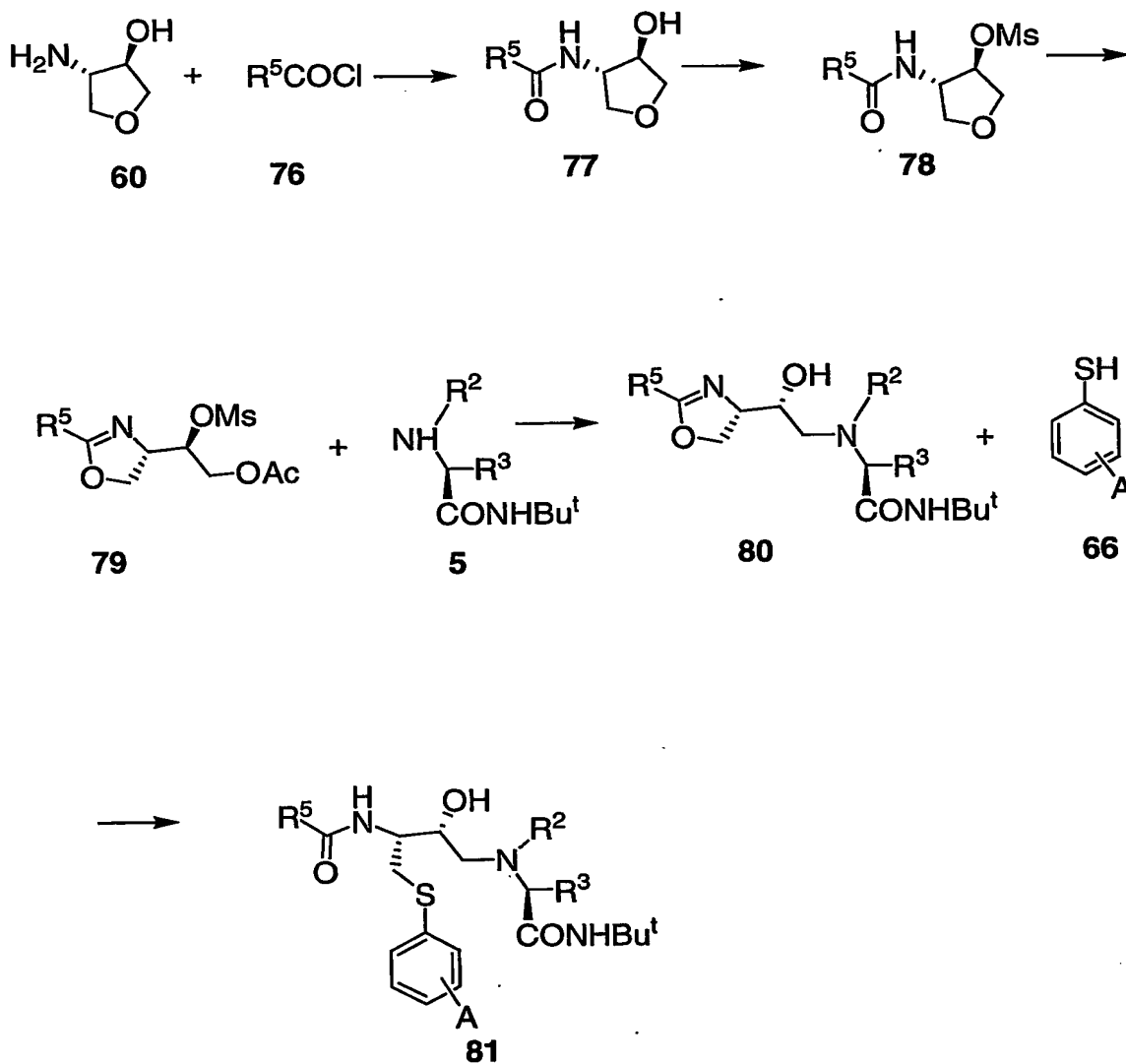
- 25 The thus-obtained thioether **82** is then transformed, using the sequence of reactions shown in Scheme 2 into the compound **81**.

The reactions shown in the above-described Schemes 4 and 5 depict the preparation of intermediates **81** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

- 30 Scheme 6 shows the conversion of the compounds **81** in which A is OH, SH, NH, into the compounds **2** in which A is link-P(O)(OR¹)₂.

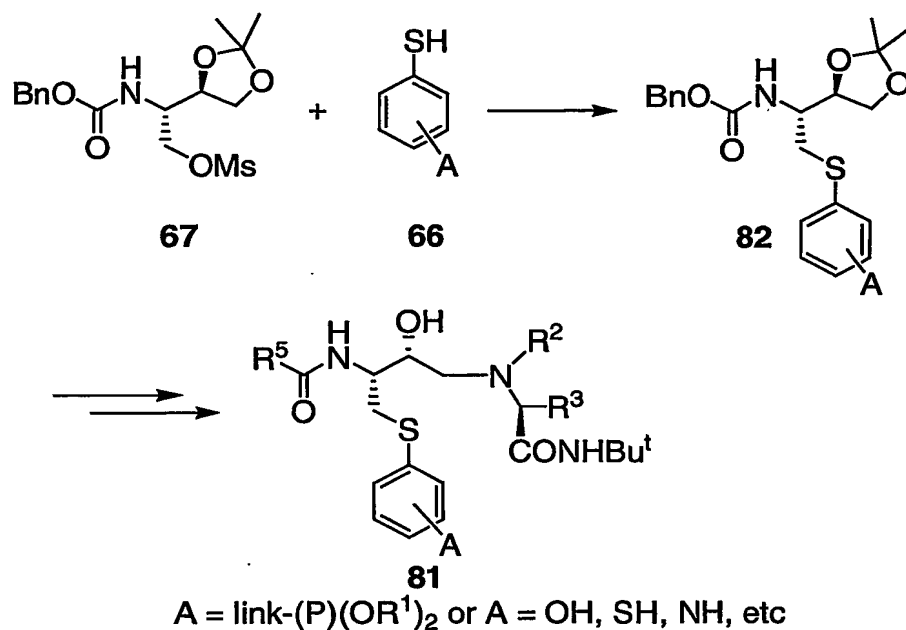
Methods for these transformations are shown in Schemes 20-48 and are discussed in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 4

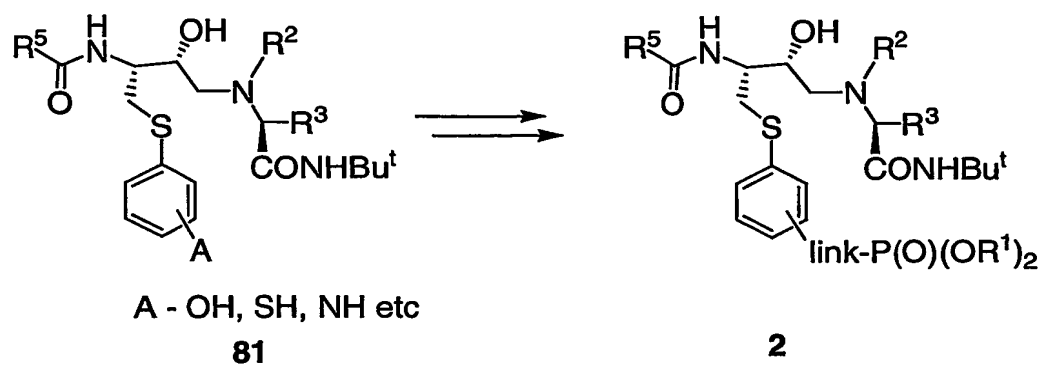


A = link-(P)(OR¹)₂ or A = OH, SH, NH, etc.

Scheme 5



Scheme 6

**Preparation of the phosphonate intermediates 3, in which X = S.**

The phosphonate intermediates 3 in which X = S, and in which the link-P(O)(OR¹)₂ group is attached to the tert. butyl moiety, are prepared as shown in Schemes 7 and 8.

As shown in Scheme 7, the isoxazolines **79**, the preparation of which are described above, are reacted with the amines **83**, using the conditions described above for the conversion of **64** to **65**, (Scheme 1) to afford the product **84**.

This compound is then converted, using the methods described above, (Scheme 1) into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compounds **85** can be prepared by the reactions shown in Scheme 8.

In this method, the oxirane **72**, the preparation of which is described above, (Scheme 2) is reacted with the amine **83**, using the reaction conditions described above for the conversion of **72** to **73** (Scheme 2), to afford the hydroxyamine **86**. This compound is then converted, using the procedures described above, into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes 7 and 8 depict the preparation of intermediates **85** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 9 shows the conversion of the compounds **85** in which A is OH, SH, NH, into the compounds **3** in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes **20** to **48** in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 4 in which X = S.

The preparations of the phosphonate intermediates **4**, in which the link-P(O)(OR¹)₂ group is attached to the decahydroisoquinoline moiety, are shown in Schemes **10** to **12**.

As shown in Scheme **10**, the isoxazoline mesylate **79**, the preparation of which is described above, (Scheme 4) is reacted with the amine **88**, the preparation of which is described below. The reaction is preformed using the procedures described above for the preparation of **65** (Scheme 1).

The reaction product **89** is then transformed, using the procedures described above, (Scheme 1) into the compound **90**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compound **90** can be prepared by the reactions shown in Scheme **11**.

In this reaction scheme, the oxirane **72**, the preparation of which is described above, (Scheme 2) is reacted with the amine **88**, using the conditions described above for the preparation of **73** (Scheme 2) to afford the hydroxyamine **91**. This compound is then converted, using the reaction schemes and conditions described above for the preparation of **1**, (Scheme 2) into the compound **90**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes **10** and **11** depict the preparation of intermediates **90** in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme **12** shows the conversion of the compounds **90** in which B is OH, SH, NH, to the compounds **4** in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes **20-48** in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 1, in which X is a direct bond

As shown in Scheme **13**, the oxirane **92**, in which X is H, the preparation of which is described in J. Med. Chem., 1997, 40, 1995, and in Bioorg. Med. Chem. Lett., 5, 2885, 1995, is reacted with the amine **5**. The compounds are reacted together using the conditions described above for the preparation of **73**, (Scheme 2) to afford the hydroxyamine **93**. This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme 2) into the compound **94**, in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme **14** shows the conversion of the compounds **94** in which A is OH, SH, NH, to the compounds **1** in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes **20-43** in which the preparations of the phosphonate-containing reactants are depicted.

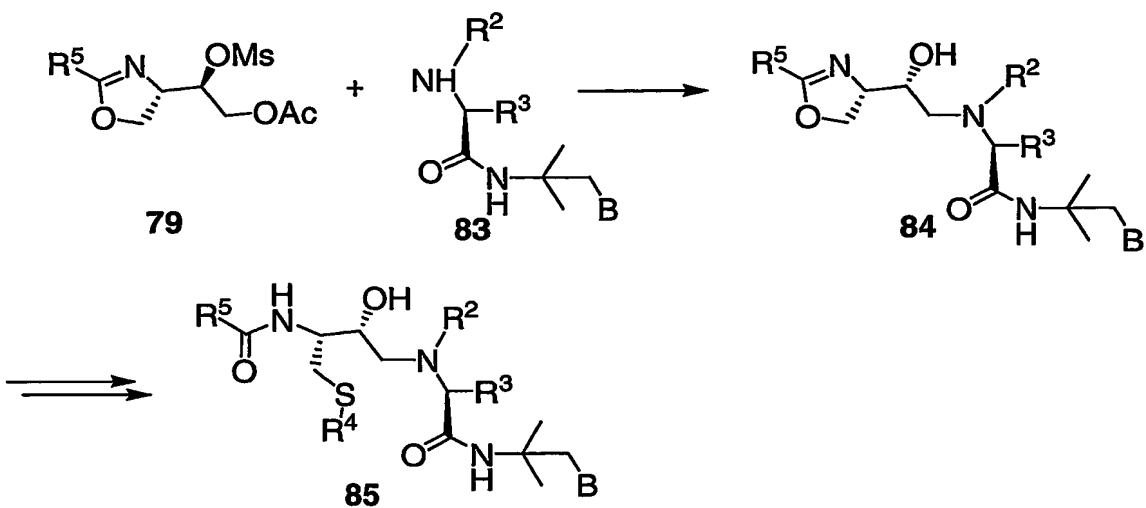
Preparation of the phosphonate intermediates 2, in which X is a direct bond.

The preparation of the compounds **2**, in which X is a direct bond, and the group link-P(O)(OR¹)₂ is attached to the phenyl ring, is illustrated in Schemes **14a** and **14b**.

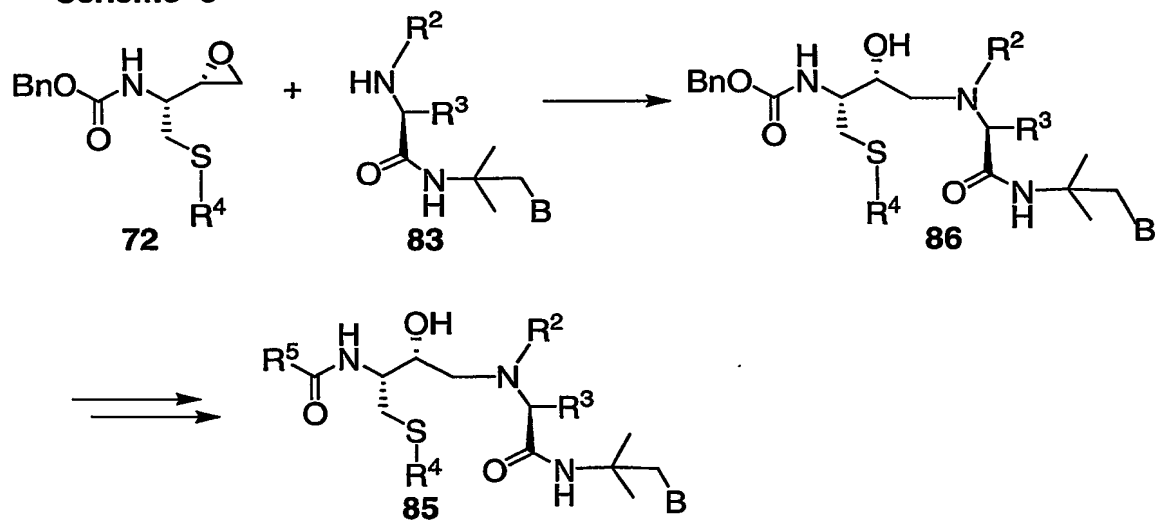
In the procedure shown in Scheme 14a, the epoxide 14a-1, prepared as described below (Scheme 45) is reacted with an amine 5, using the conditions described above for the preparation of the hydroxyamine 73 (Scheme 2), to afford the hydroxyamine 14a-2.

The latter compound, after removal of the BOC protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Third Edition 1999, p. 520-522, is then converted, by reaction with the carboxylic acid R^5COOH , or an activated derivative thereof, into the amide 14a-3. The conditions for this reaction are the same as those described above for the preparation of the amide 62, (Scheme 1).

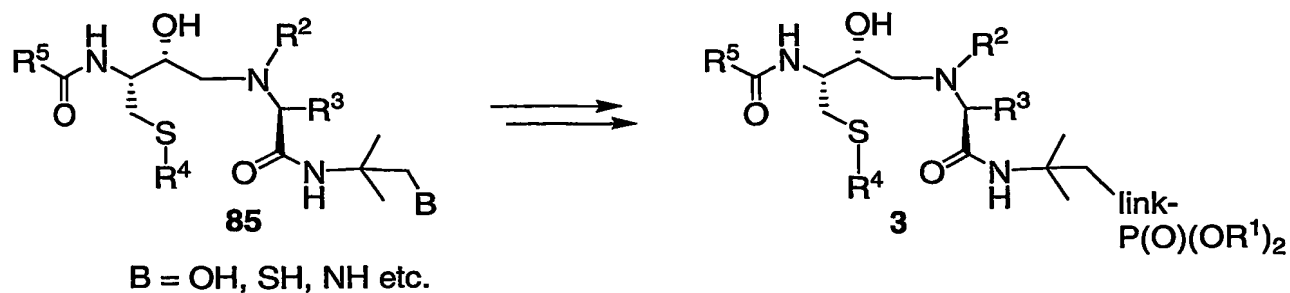
The reactions shown in Scheme 14a illustrate the preparation of the compounds 14a-3 in which A is either the group link-P(O)(OR¹)₂ or a precursor thereto such as OH, SH, NH₂. Scheme 14b illustrates the conversion of the compounds 14a-3, in which A is OH, SH, NH₂, into the compounds 2 in which A is the group link-P(O)(OR¹)₂. The methods for this transformation are described below in Schemes 20-48, in which the preparation of the phosphonate-containing reactants are described.

Scheme 7

B = link-(P)(OR¹)₂ or B = OH, SH, NH etc.

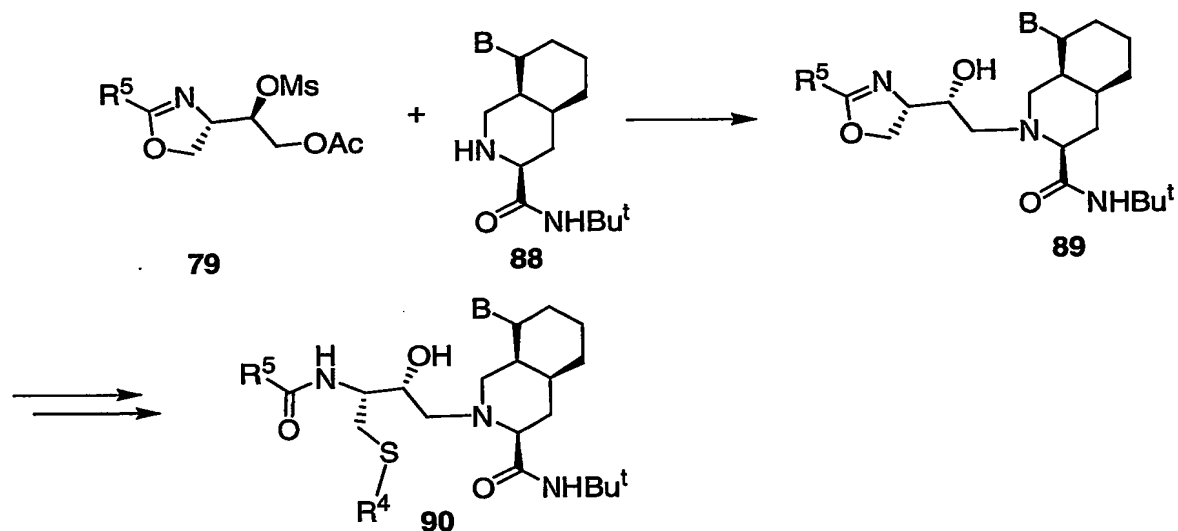
Scheme 8

B = link-(P)(OR¹)₂ or B = OH, SH, NH etc.

Scheme 9

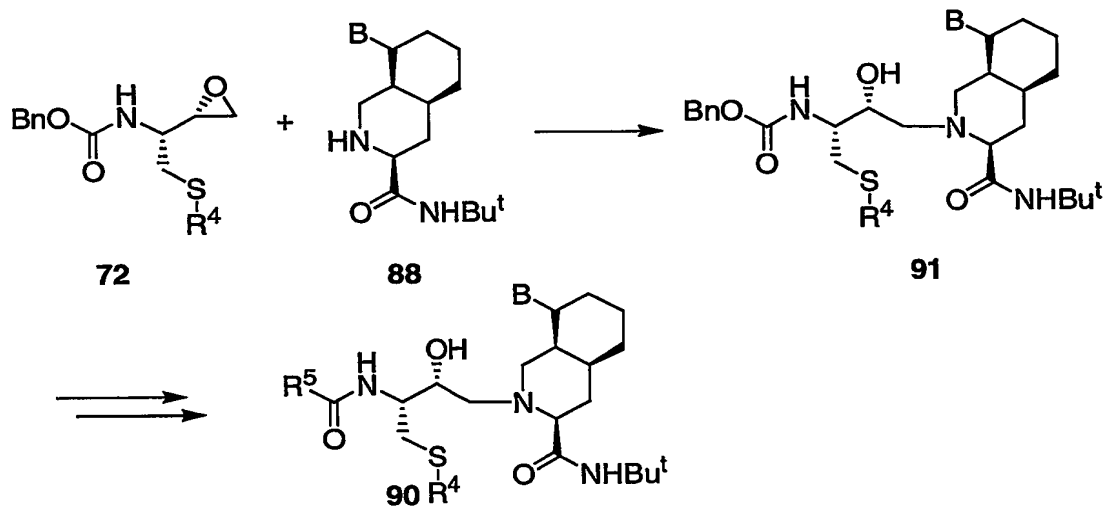
B = OH, SH, NH etc.

Scheme 10



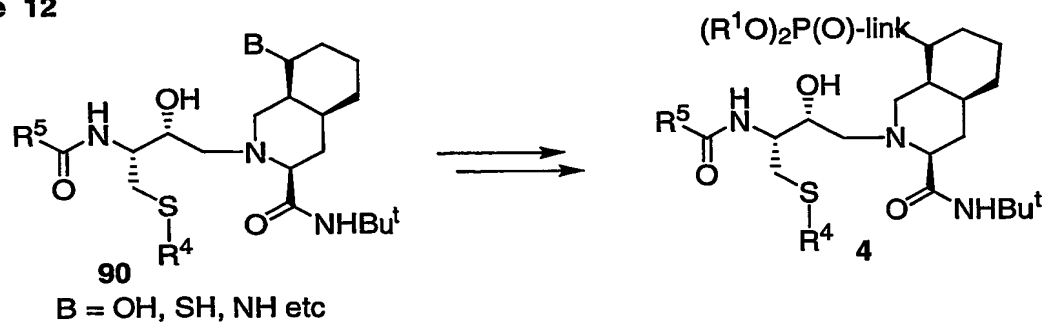
B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

Scheme 11



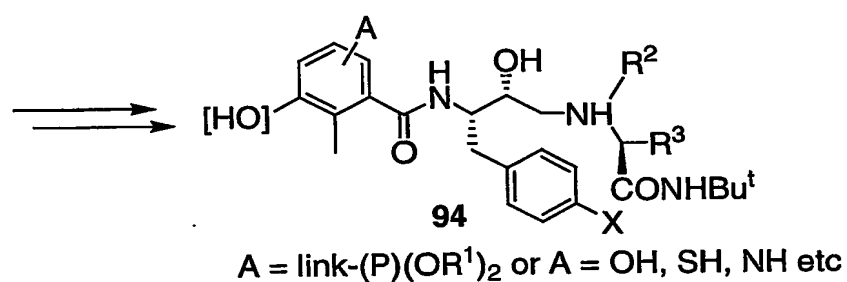
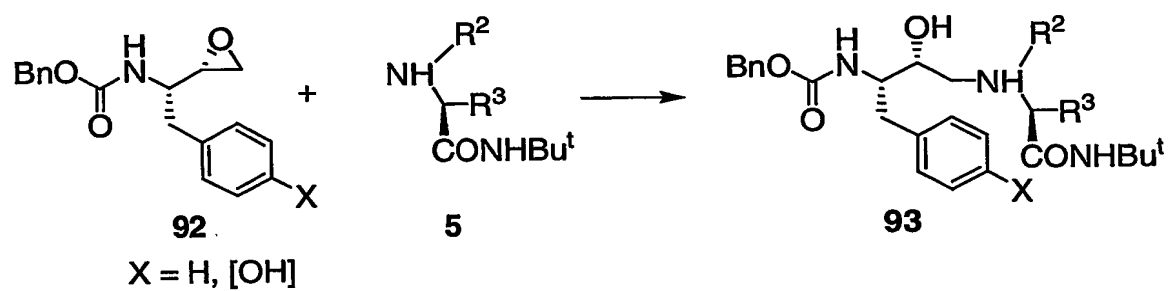
B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

Scheme 12

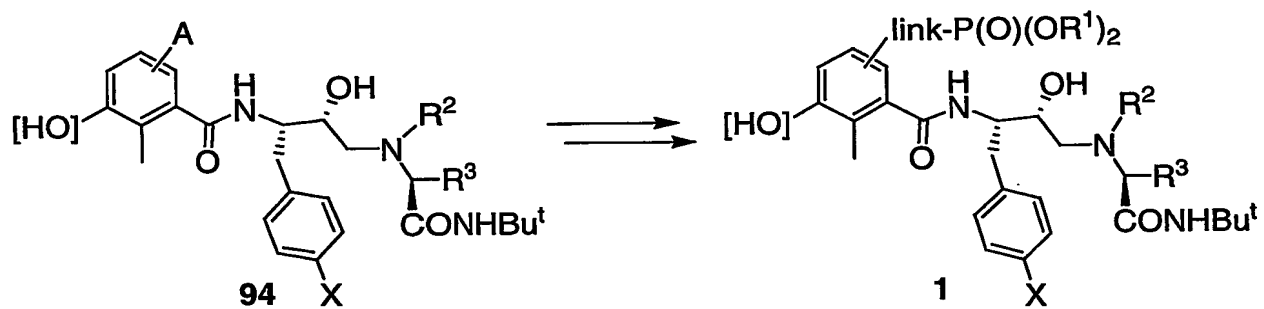


B = OH, SH, NH etc

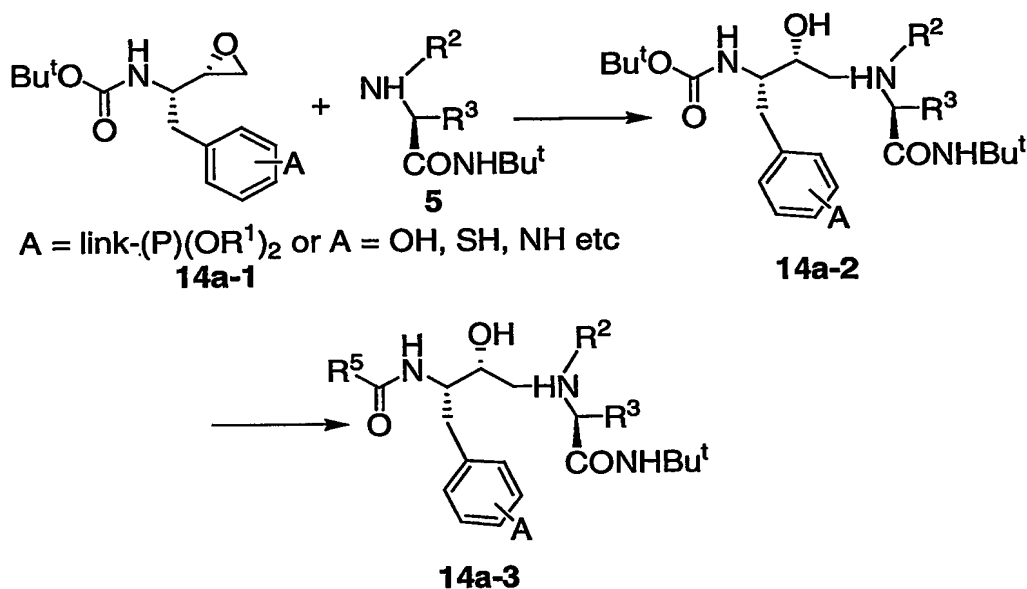
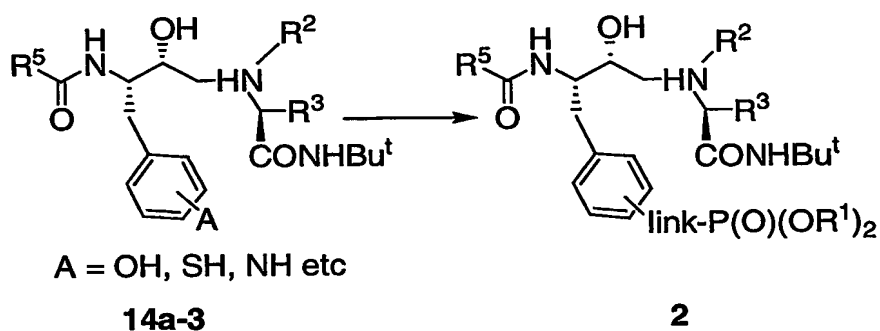
Scheme 13



Scheme 14



X = H, [OH] A = OH, SH, NH₂ etc

Scheme 14a**Scheme 14b****Preparation of the phosphonate intermediates 3, in which X is a direct bond.**

As shown in Scheme 15, the oxirane **92**, in which X is H, is reacted with the amine **83**, in which the phosphonate or precursor group is attached to the tert. butyl group, to afford the product **95**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme 2) into the compound **96**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 16 shows the conversion of the compounds **96** in which B is OH, SH, NH, to the compounds **3** in which B is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

5

Preparation of the phosphonate intermediates 4, in which X is a direct bond.

As shown in Scheme 17, the oxirane **92** is reacted with the amine **88**, in which the phosphonate or precursor group is attached to the decahydroisoquinoline moiety, to afford the product **97**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme 2) into the compound **98**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

10

15

Scheme 18 shows the conversion of the compounds **98** in which B is OH, SH, NH, into the compounds **4** in which B is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

Schemes 13-18 illustrate the preparations of the compounds **1**, **3** and **4**, in which X is a direct bond, and in which the phenyl ring is either unsubstituted or incorporates a protected hydroxyl group at the 4-position.

20

Scheme 19 depicts the synthesis of compounds **1**, **3** and **4**, in which X is a direct bond, and in which the phenyl ring incorporates different substituents, as described above (Chart 3) in the 4-position.

25

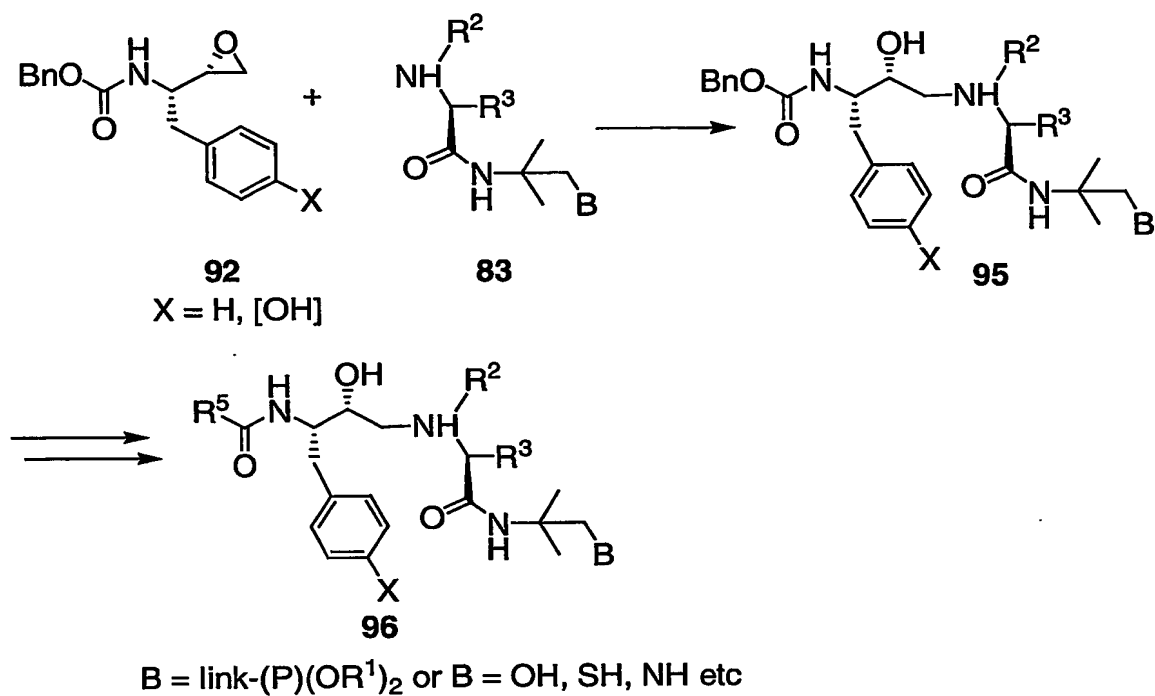
In this procedure, [2-(4-hydroxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester **99**, the preparation of which is described in U.S. Patent 5,492,910, is reacted with an appropriate alkylating agent, such as, for example, ethyl iodide, benzyl chloride, bromoethyl morpholine or bromoacetyl morpholine. The reaction is conducted in an aprotic solvent, such as, for example, dichloromethane or dimethylformamide, in the presence of an organic or inorganic base.

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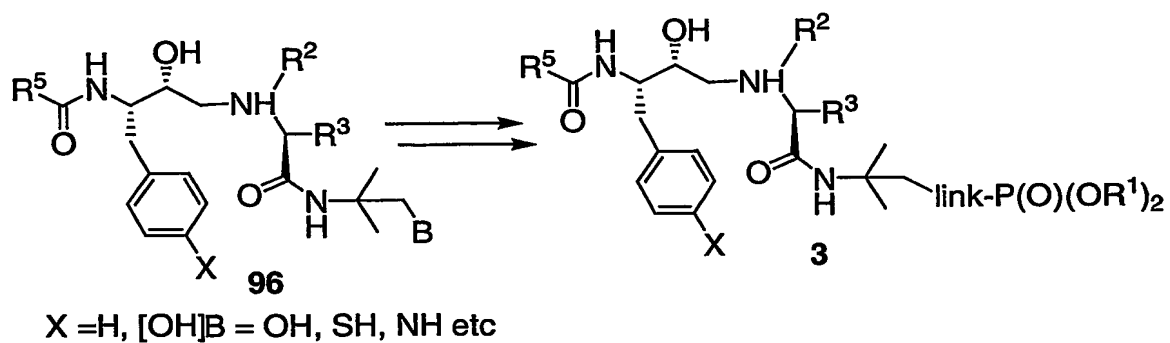
Preferably the hydroxy compound **99** is reacted with an equimolar amount of the alkylating agent in dichloromethane, in the presence of diisopropylethylamine, at ambient temperature, so as to afford the ether products **100**. The compounds **100** are then transformed, using the

conditions described above for the reactions depicted in Schemes 13-18, into the products 1, 3 and 4, in which X is a direct bond, and in which R is as defined in Scheme 19.

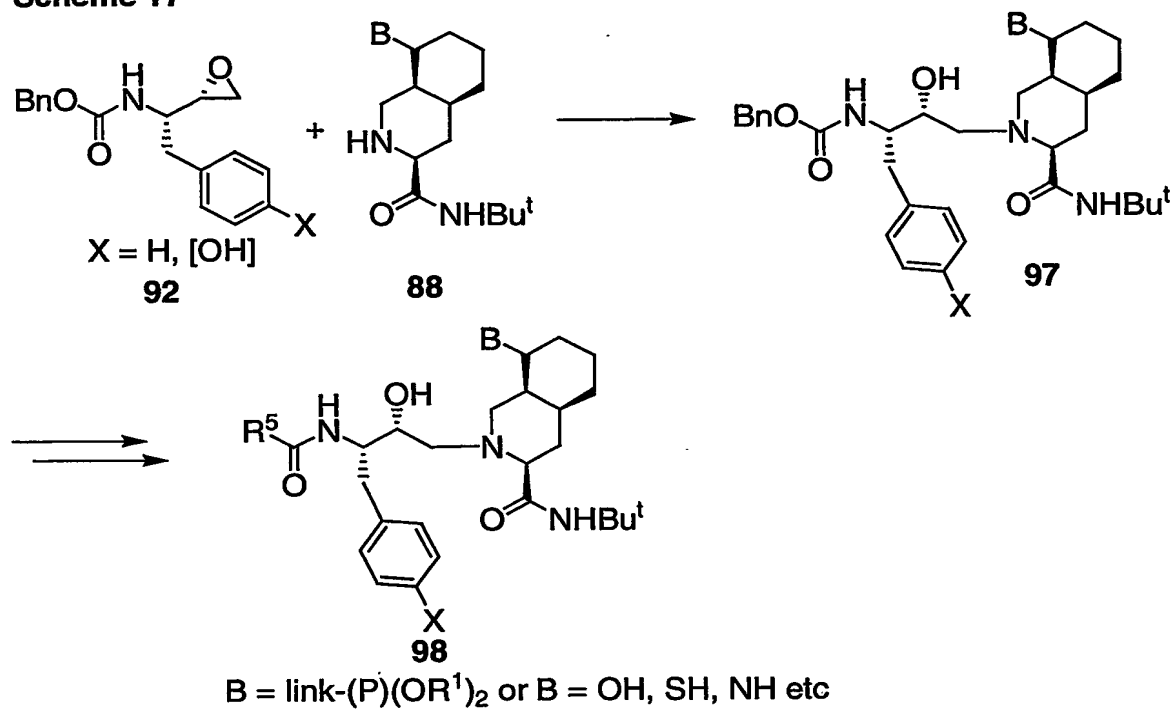
Scheme 15



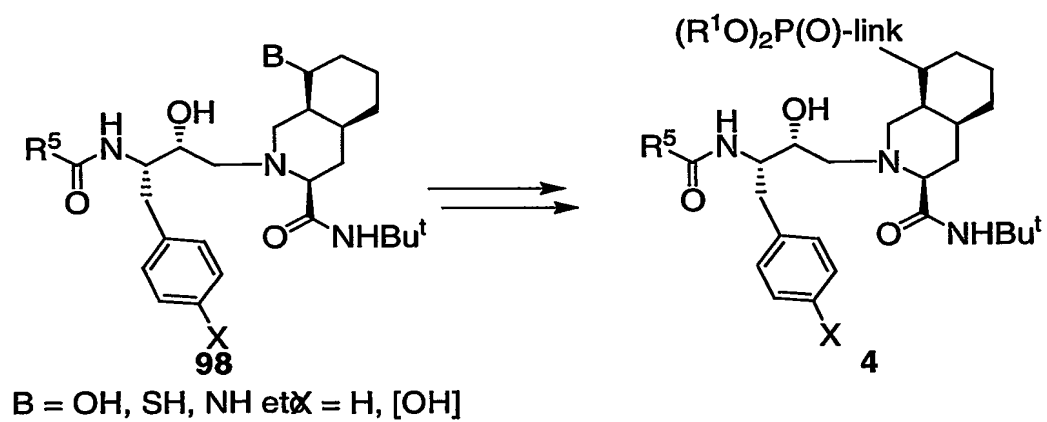
Scheme 16



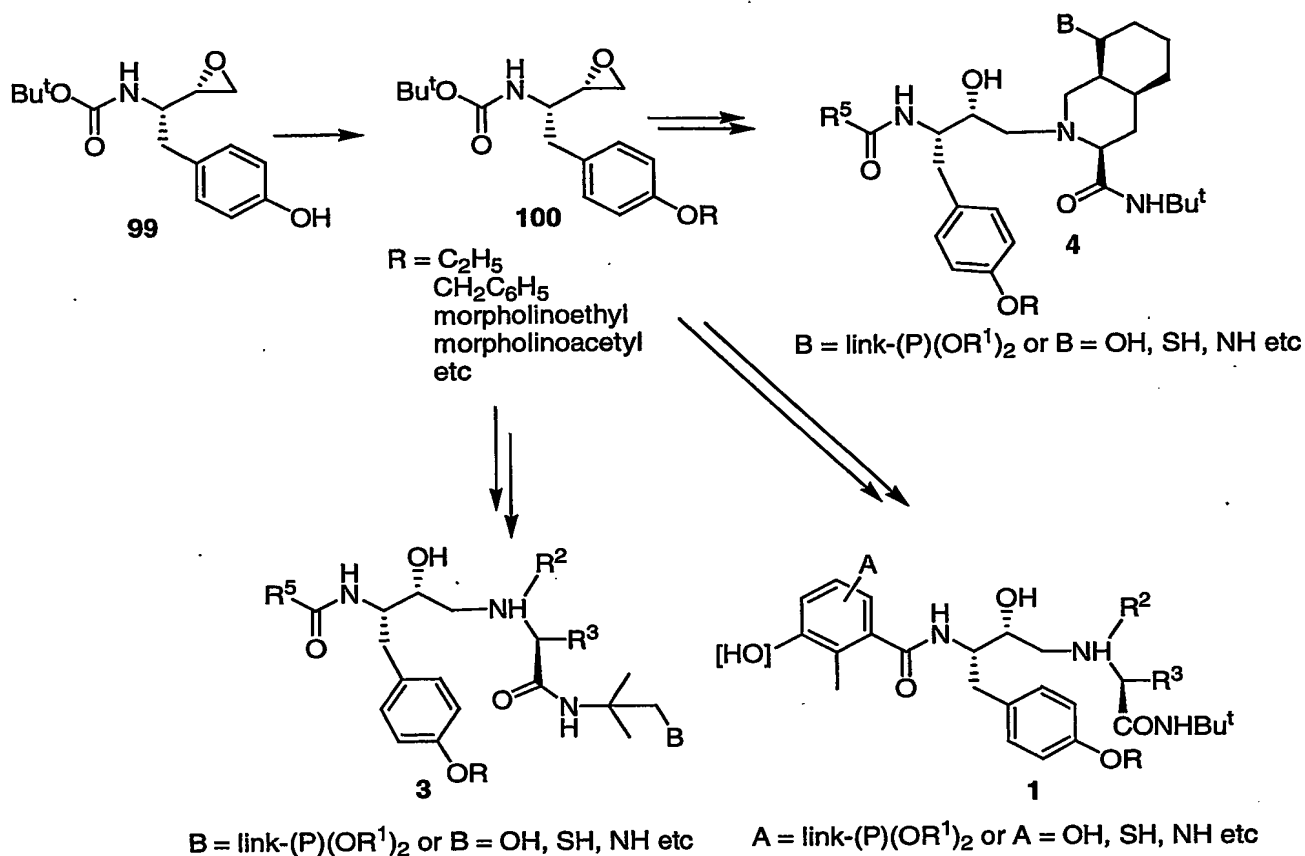
Scheme 17



Scheme 18



Scheme 19



Nel10b.cdx Schemes 19a, 19b

5 Preparation of thiophenol derivatives R^4SH incorporating phosphonate substituents

Various methods for the preparation of thiols are described in *The Chemistry of the Thiol Group*, S. Patai, Ed., Wiley, 1974, Vol. 14, Part 3, p 42.

10 Protection/deprotection of SH groups.

The preparations of thiophenols incorporating phosphonate moieties are shown in Schemes 20-30. In order to avoid unwanted reactions, it may be necessary to protect the SH group, and to deprotect it after the transformations shown. Protected SH groups are shown in the Schemes as [SH]. The protection and deprotection of SH groups is described in a number of publications. For example, in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 277-308, are described the introduction and removal of a

number of SH protecting groups. The selection of a SH protecting group for a given series of reactions requires that it be stable to the reaction conditions employed, and that the protecting group can be removed at the end of the reaction sequence without the occurrence of undesired reactions. In the following descriptions, appropriate protection and deprotection methods are indicated.

Scheme 20 illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring.

In this procedure, a halo-substituted thiophenol is subjected to a suitable protection procedure.

The protected compound 101 is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite 102, to afford the product 103. The product is then deprotected to afford the free thiophenol 104.

Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert

solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992.

Preferably, the 3-bromothiophenol 105 is protected by conversion to the 9-fluorenylmethyl derivative, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 284, and the product 106 is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product 108. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol 109.

Using the above procedures, but employing, in place of the bromo compound 105, different bromo compounds 101, there are obtained the corresponding thiols 104.

Scheme 21 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 101 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 110. The latter compound is reacted with a halodialkyl phosphate 111 to afford the product 103.

Preferably, the 4-bromothiophenol 112 is converted into the S-triphenylmethyl (trityl) derivative 113, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **114** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **115** to afford the phosphonate **116**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **117**.
Using the above procedures, but employing, in place of the halo compound **112**, different halo compounds **101**, there are obtained the corresponding thiols **104**.

Scheme 22 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link.

In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **118**. This compound is reacted with a sodium dialkyl phosphite **119** or a trialkyl phosphite, to give the displacement or rearrangement product **120**, which upon deprotection affords the thiophenols **121**.

Preferably, 2-methylthiophenol **123** is protected by conversion to the benzoyl derivative **124**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **125**. This material is reacted with a sodium dialkyl phosphite **119**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **126**. Alternatively, the bromomethyl compound **125** can be converted into the phosphonate **126** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **125** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **126**. Deprotection of **126**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **127**.

Using the above procedures, but employing, in place of the bromomethyl compound **125**, different bromomethyl compounds **118**, there are obtained the corresponding thiols **121**.

Scheme 23 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **128** is reacted with a dialkyl hydroxyalkylphosphonate **129** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product **130**. Deprotection then yields the O- or S-linked products **131**.

Preferably, the substrate, for example 3-hydroxythiophenol, **132**, is converted into the monotrityl ether **133**, by reaction with one equivalent of trityl chloride, as described above.

5 This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **134** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **135**. Removal of the trityl protecting group, as described above, then affords the thiophenol **136**.

10 Using the above procedures, but employing, in place of the phenol **132**, different phenols or thiophenols **128**, there are obtained the corresponding thiols **131**.

Scheme 24 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **137** is reacted with an activated ester, for example the trifluoromethanesulfonate, of a dialkyl hydroxyalkyl phosphonate **138**, to afford the coupled
15 product **139**. Deprotection then affords the thiol **140**.

For example, the substrate, 4-methylaminothiophenol **141**, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **142**. This material is then reacted with, for example, diethyl trifluoromethanesulfonylmethyl phosphonate **143**, the preparation of
20 which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **144**.

Preferably, equimolar amounts of the phosphonate **143** and the amine **142** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **144**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer.
25 Chem. Soc., 85, 1337, 1963, then affords the thiophenol **145**.

Using the above procedures, but employing, in place of the thioamine **142**, different phenols, thiophenols or amines **137**, and/or different phosphonates **138**, there are obtained the corresponding products **140**.

Scheme 25 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 146.

In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 137 is reacted with a dialkyl bromoalkyl phosphonate 146 to afford the product 147. Deprotection then affords the free thiophenol 148.

For example, 3-hydroxythiophenol 149 is converted into the S-trityl compound 150, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 151, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 152. Deprotection, as described above, then affords the thiol 153.

Using the above procedures, but employing, in place of the phenol 149, different phenols, thiophenols or amines 137, and/or different phosphonates 146, there are obtained the corresponding products 148.

Scheme 26 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 155 is coupled with an aromatic bromo compound 154. In this procedure, a suitably protected bromo-substituted thiophenol 154 is reacted with a terminally unsaturated phosphonate 155, to afford the coupled product 156. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 157, or the saturated analog 159.

For example, 3-bromothiophenol is converted into the S-Fm derivative 160, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate 161, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for

example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **162**. Deprotection, as described above, then affords the thiol **163**.

Optionally, the initially formed unsaturated phosphonate **162** can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product **164**, which upon deprotection affords the thiol **165**.

Using the above procedures, but employing, in place of the bromo compound **160**, different bromo compounds **154**, and/or different phosphonates **155**, there are obtained the corresponding products **157** and **159**.

Scheme **28** illustrates the preparation of an aryl-linked phosphonate ester **169** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

The sulfur-substituted phenylboronic acid **166** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **168** which is deprotected to yield the thiol **169**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **170**. This material is reacted with diethyl 4-bromophenylphosphonate **171**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **172**. Deprotection, for example by the use of tetrabutyl ammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **173**.

Using the above procedures, but employing, in place of the boronate **170**, different boronates **166**, and/or different phosphonates **167**, there are obtained the corresponding products **169**.

Scheme 29 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring.

In this procedure, a suitably protected O, S or N-substituted thiophenol 137 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 174, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 175 is then deprotected to afford the thiol 176. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester 177 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 177 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 178, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 179 thus obtained is deprotected, as described above, to afford the thiol 180.

Using the above procedures, but employing, in place of the thiophenol 177, different phenols, thiophenols or amines 137, and/or different phosphonates 174, there are obtained the corresponding products 176.

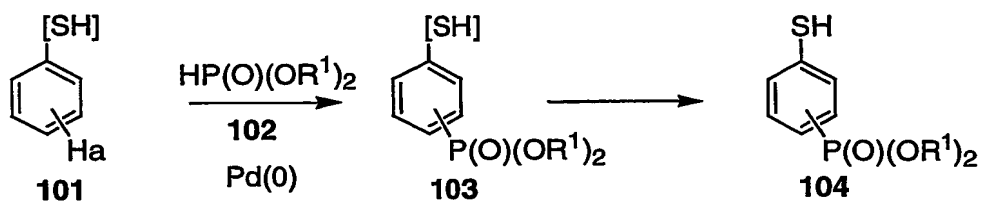
Scheme 30 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol 181, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 138, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 182. Deprotection, as described above, then affords the thiol 183. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

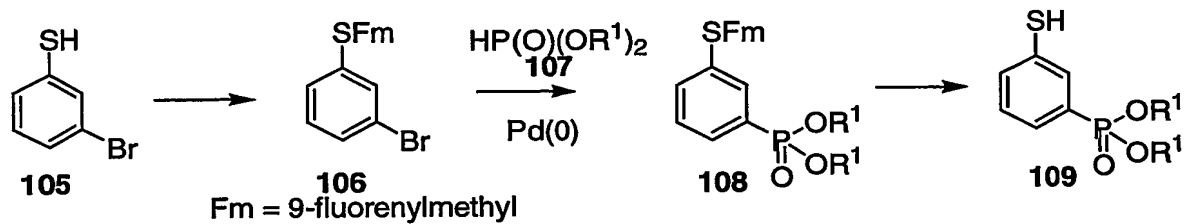
J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al., eds., Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **184**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **185**, as described above, and the ester is then reacted with the triflate **143**, using the conditions described above for the preparation of **144**, (Scheme **24**), to yield the phosphonate **186**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **187**. Using the above procedures, but employing, in place of the thiol **184**, different thiols **181**, and/or different triflates **138**, there are obtained the corresponding products **183**.

Scheme 20

Method

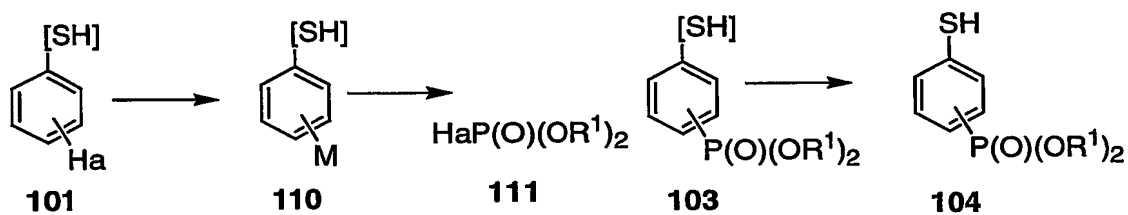


Example

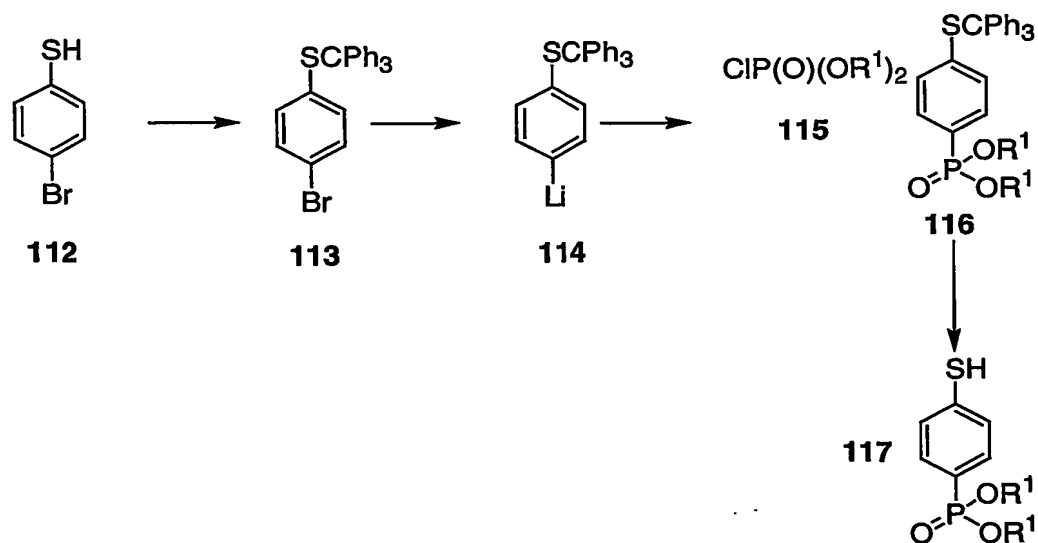


Scheme 21

Method

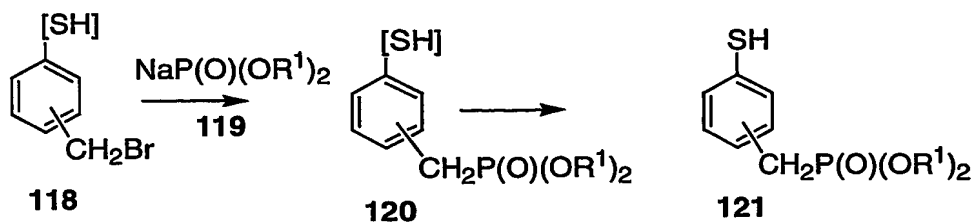


Example

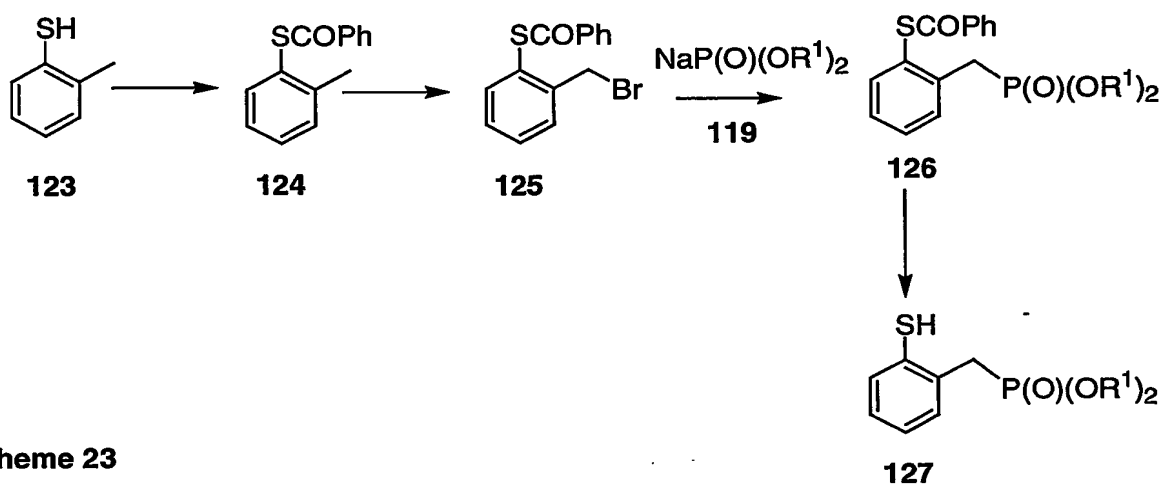


Scheme 22

Method

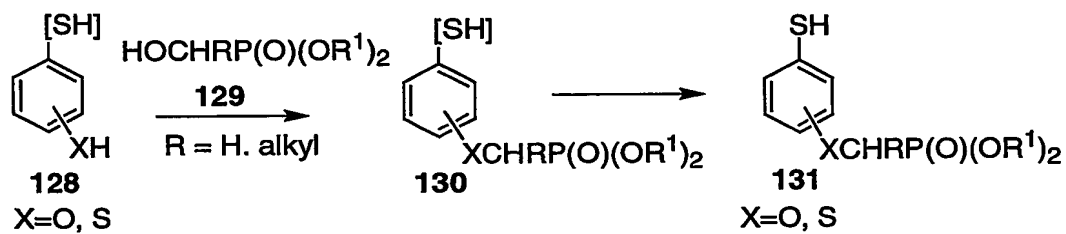


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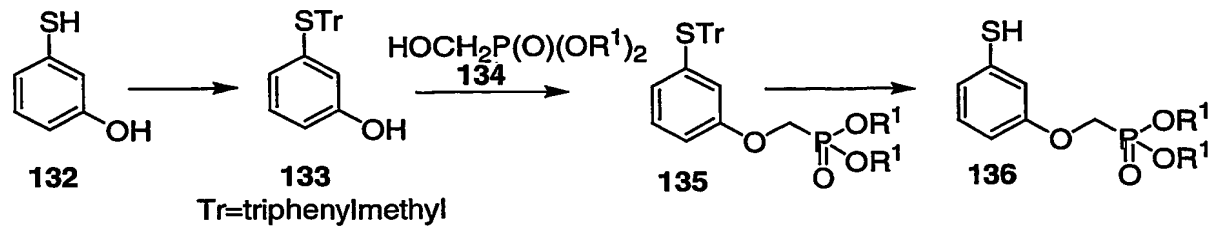


Scheme 23

Method

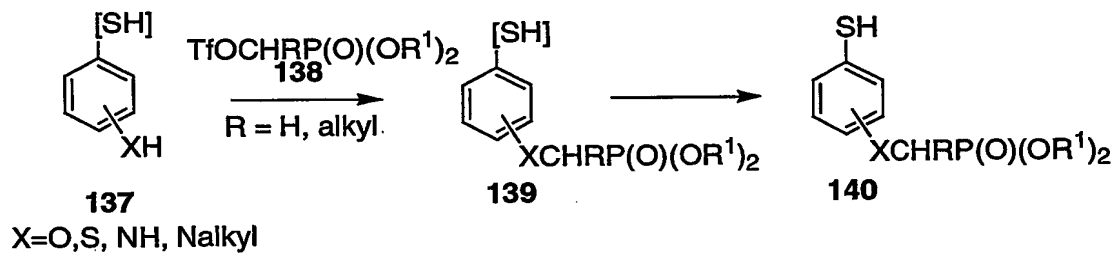


Example

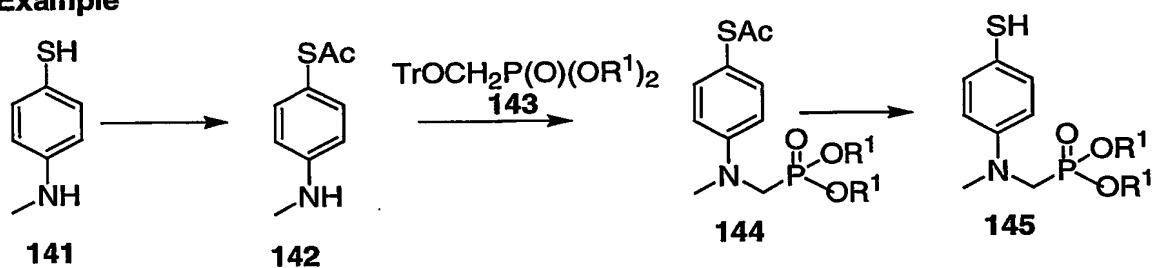


Scheme 24

Method

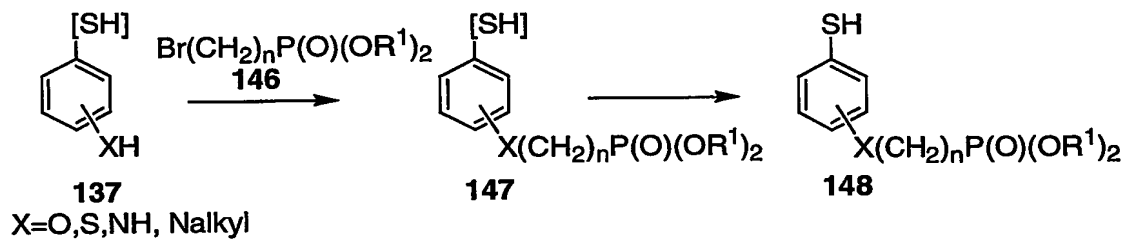


Example

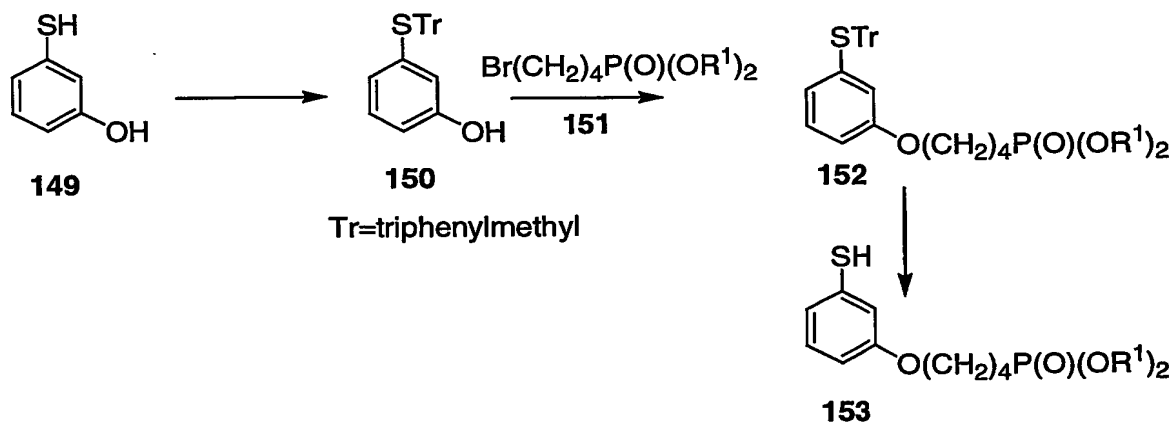


Scheme 25

Method

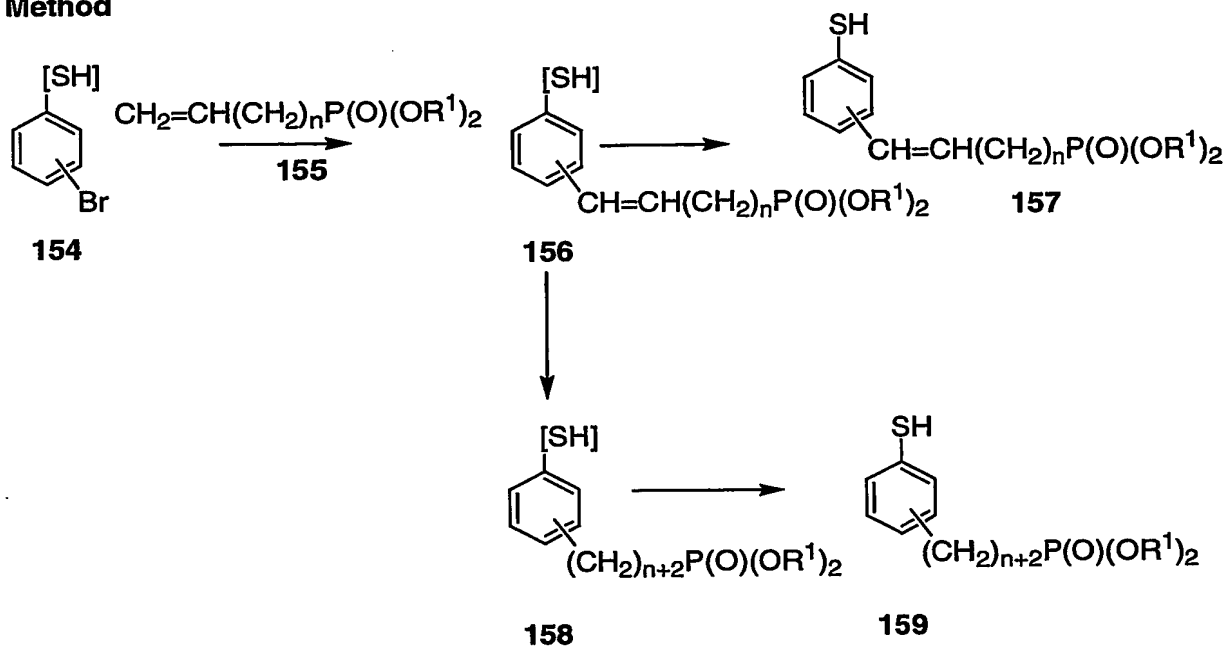


Example

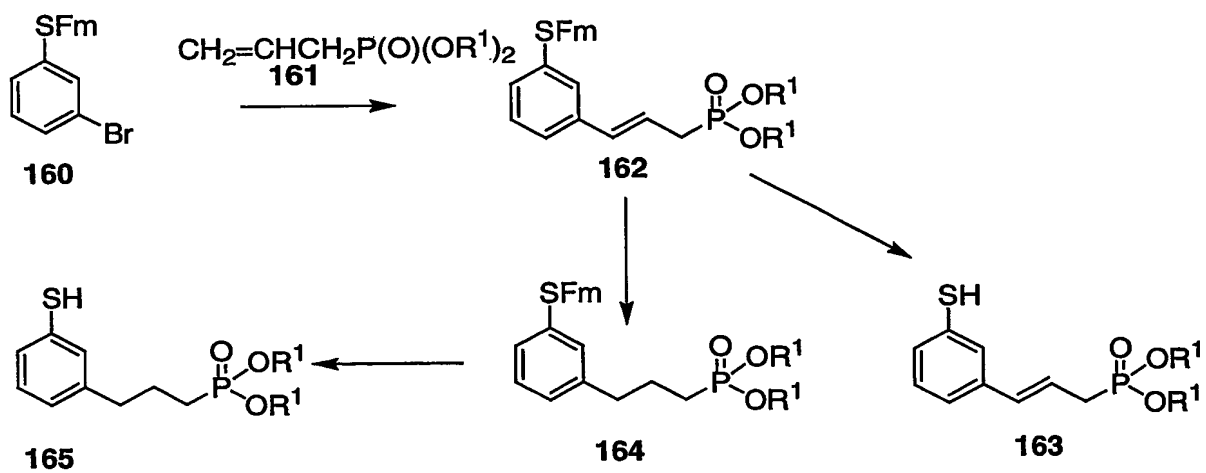


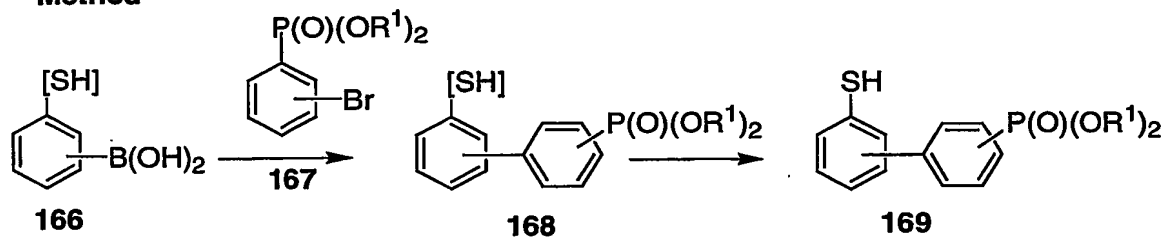
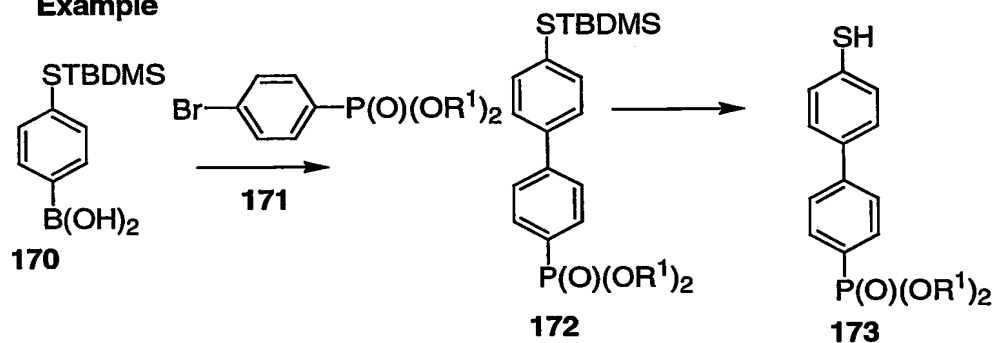
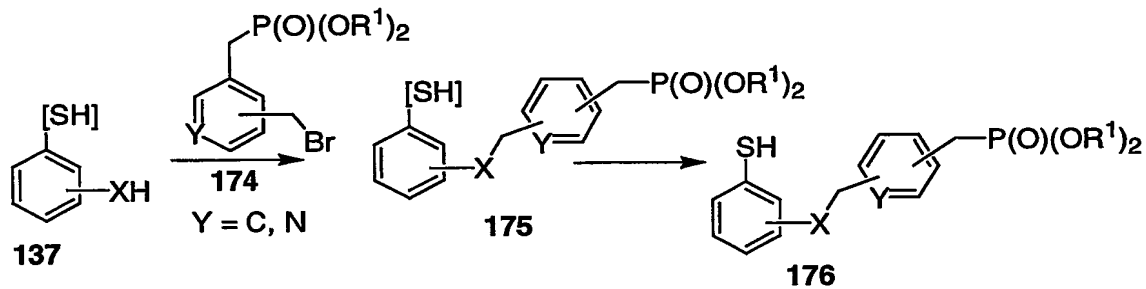
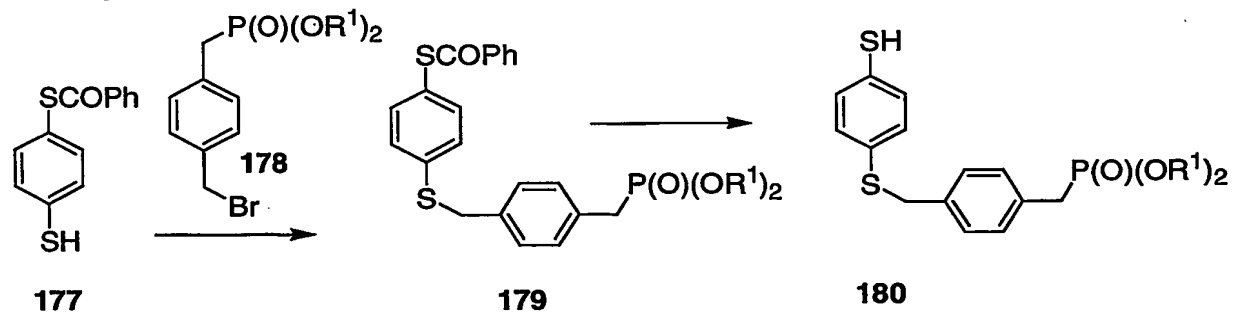
Scheme 26

Method



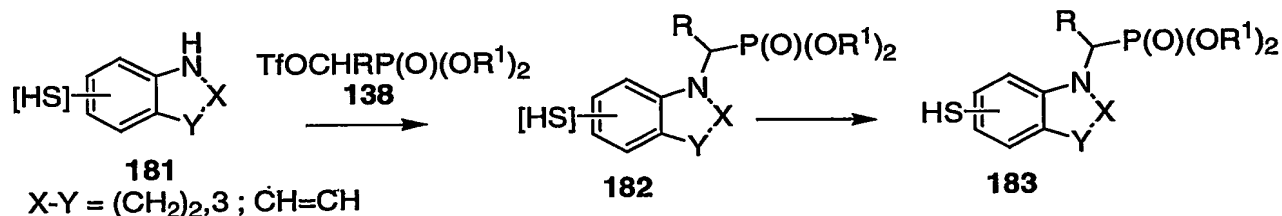
Example



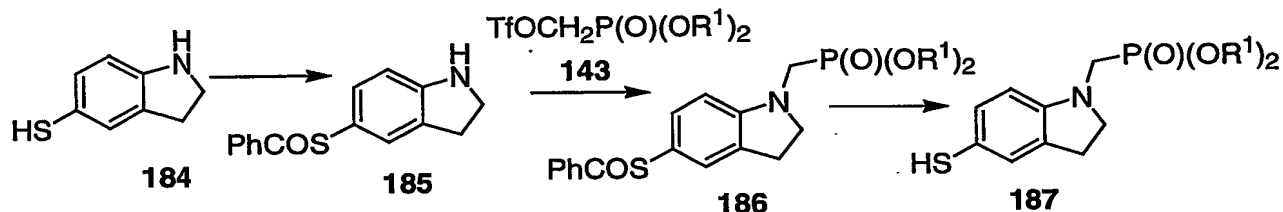
Scheme 28**Method****Example****Scheme 29****Method****Example**

Scheme 30

Method



Example



Preparation of benzoic acid derivatives incorporating phosphonate moieties.

Scheme 31 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **188** is subjected to halogen-methyl exchange to afford the organometallic intermediate **189**. This compound is reacted with a chlorodialkyl phosphite **115** to yield the phenylphosphonate ester **190**, which upon deprotection affords the carboxylic acid **191**.

- For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **192**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **193**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **194**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **195**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **196**. Halogen-metal exchange is performed by the reaction of **196** with butyllithium, and the lithiated intermediate is then coupled with a

chlorodialkyl phosphite **115**, to produce the phosphonate **197**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **198**.

- 5 Using the above procedures, but employing, in place of the bromo compound **192**, different bromo compounds **188**, there are obtained the corresponding products **191**.

Scheme **32** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

- 10 In this method, a suitably protected dimethyl hydroxybenzoic acid, **199**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **200** is reacted with a sodium dialkyl phosphite, **119**, to effect displacement of the benzylic bromide to afford the phosphonate **201**.

- For example, 2,5-dimethyl-3-hydroxybenzoic acid, **203**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 17, to afford the ether ester **204**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **204** is then reacted with a brominating agent, for example 20 N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **205**. This compound is then reacted with a sodium dialkyl phosphite **119**, using the conditions described above for the preparation of **120**, (Scheme **22**) to afford the phosphonate **206**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields 25 the carboxylic acid **207**.

Using the above procedures, but employing, in place of the methyl compound **203**, different methyl compounds **199**, there are obtained the corresponding products **202**.

- Scheme **33** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

30 In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid **208** is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl

hydroxymethyl phosphonate **134**, to afford the coupled product **209**, which upon deprotection affords the carboxylic acid **210**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **211**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **212**, by

5 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, using the conditions described above for the preparation of **170**, to afford the mono-silyl ether **213**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **134**, under the
10 conditions of the Mitsunobu reaction, as described above for the preparation of **130**, (Scheme 23) to afford the coupled product **214**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **215**.

Using the above procedures, but employing, in place of the phenol **211**, different phenols or
15 thiophenols **208**, there are obtained the corresponding products **210**.

Scheme 34 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate **216** is coupled, by means of a palladium
20 catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **217**. The product **218** can be deprotected to afford the phosphonate **219**, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid **220**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **221**, prepared as described in
25 WO 9218490, is converted as described above, into the silyl ether OBO ester **222**. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **223**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above for the preparation of **156**, (Scheme 26) to afford the product **224**.

Deprotection, or hydrogenation/deprotection, of this compound, as described above, then
30 affords respectively the unsaturated and saturated products **225** and **227**.

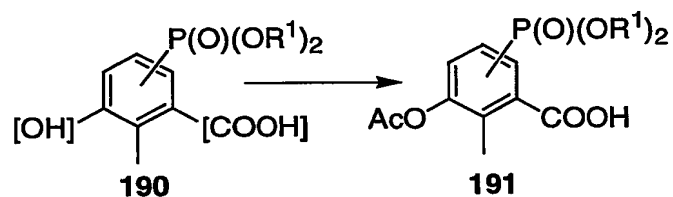
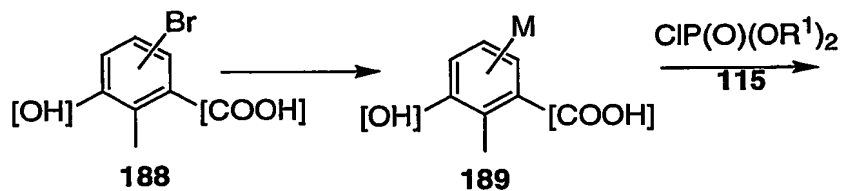
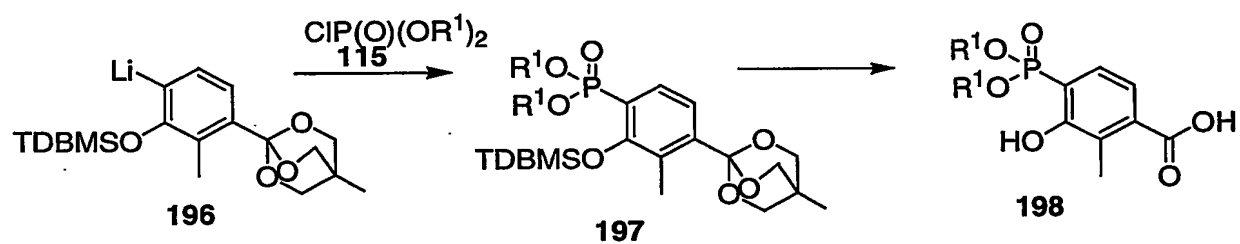
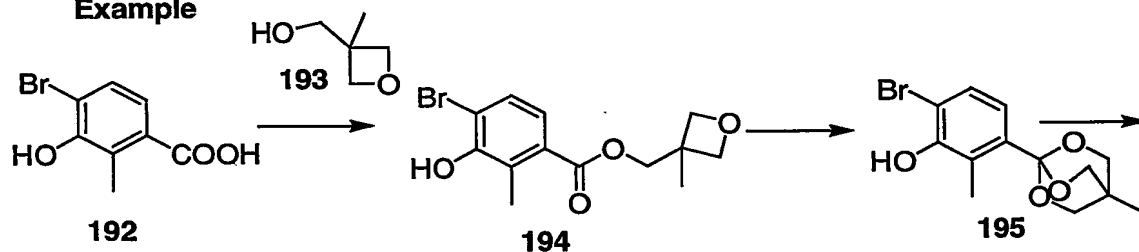
Using the above procedures, but employing, in place of the bromo compound **221**, different bromo compounds **217**, and/or different phosphonates **216**, there are obtained the corresponding products **219** and **220**.

5 Scheme **35** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **217** is converted to the corresponding boronic acid, as described above, (Scheme **28**). The product is subjected to a Suzuki coupling reaction, as described above, with a dialkyl bromophenyl phosphonate **229**. The product **230** is then deprotected to afford the diaryl phosphonate product **231**.

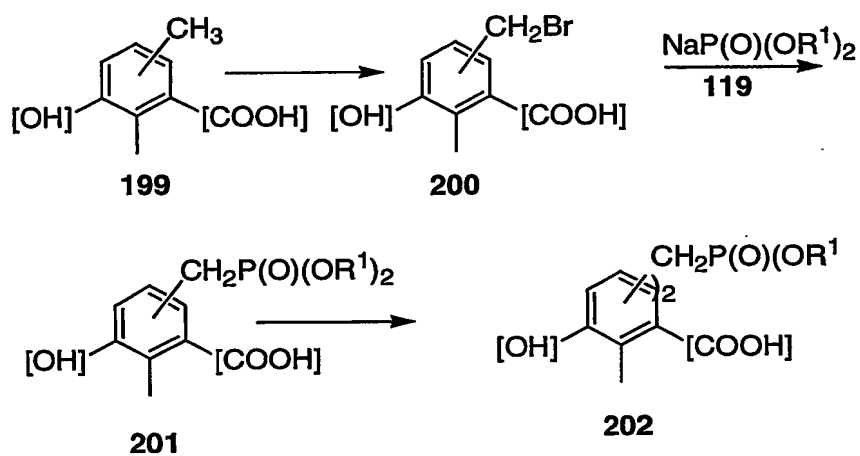
For example, the silylated OBO ester **232**, prepared as described above, (Scheme **31**), is converted into the boronic acid **233**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **234**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, as described above for the preparation of **172**, (Scheme **28**) to afford the diaryl phosphonate **235**. Deprotection, as described above, then affords the benzoic acid **236**.

Using the above procedures, but employing, in place of the bromo compound **232**, different bromo compounds **217**, and/or different phosphonates **229**, there are obtained the corresponding carboxylic acid products **231**.

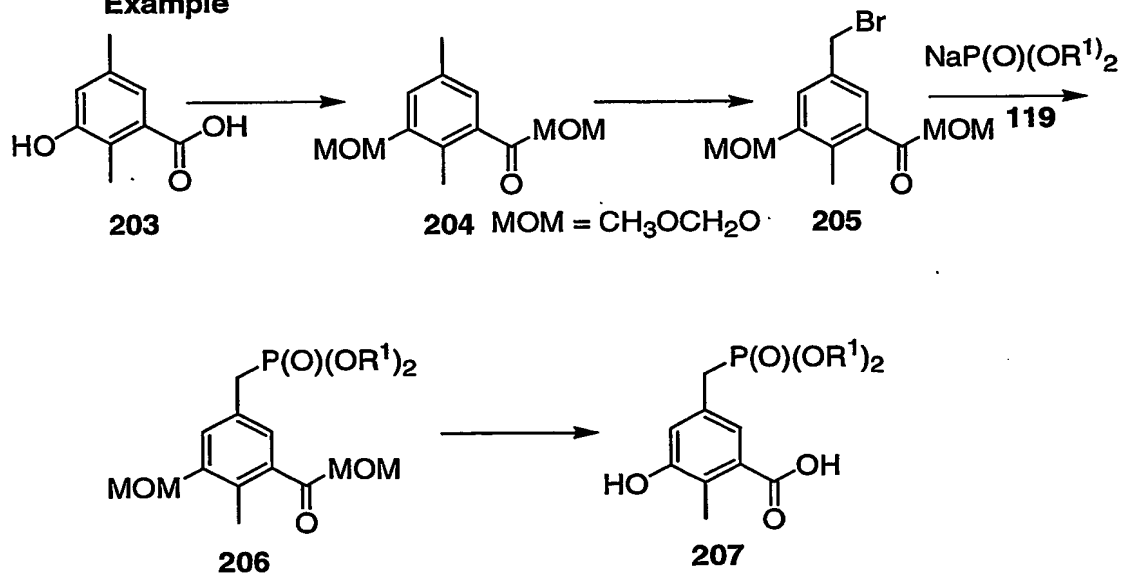
Scheme 31**Method****Example**

Scheme 32

Method

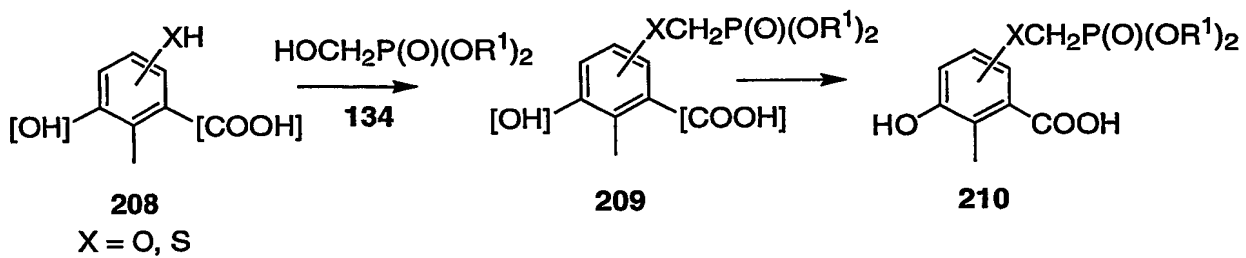


Example

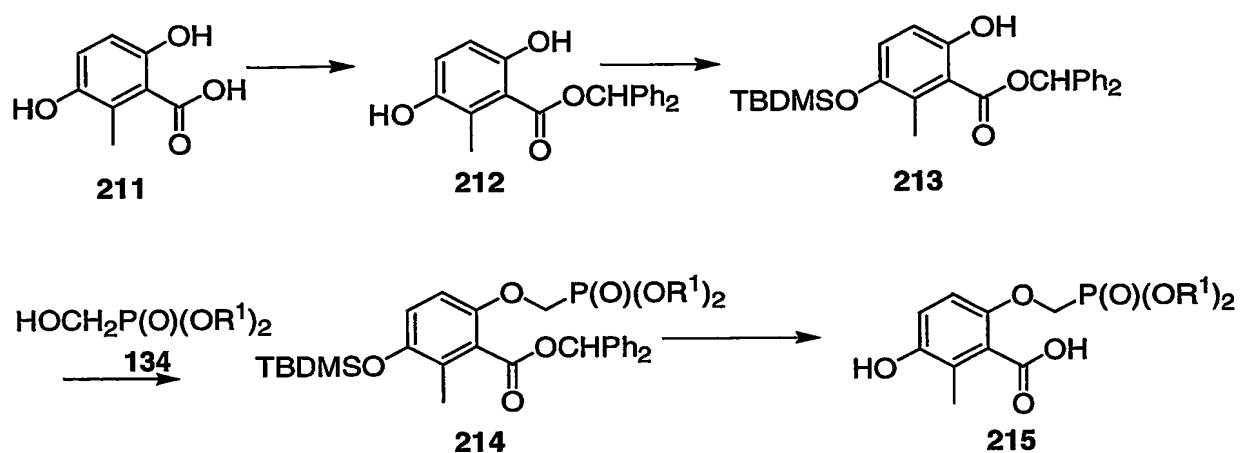


Scheme 33

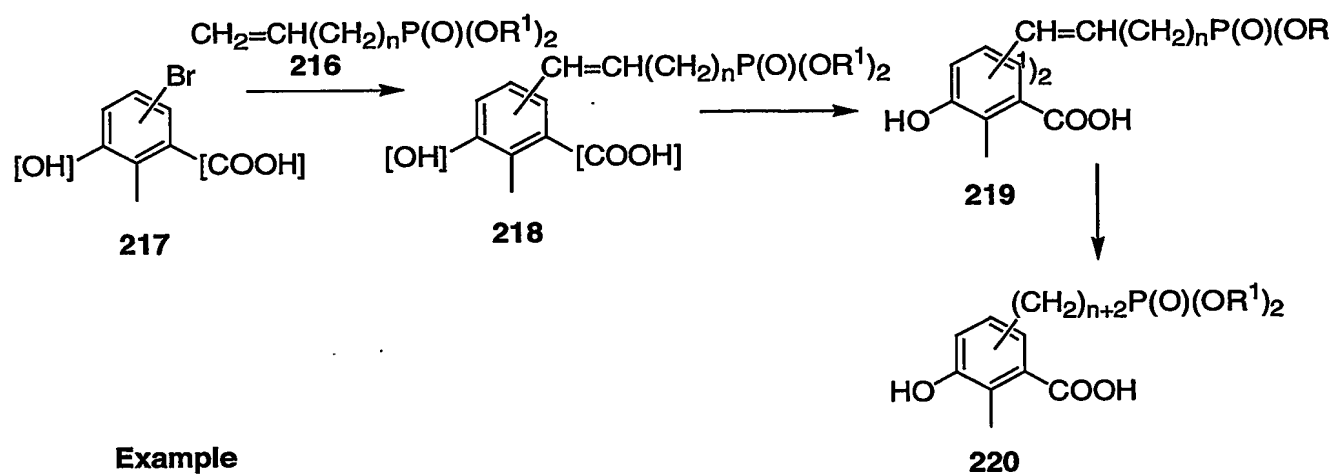
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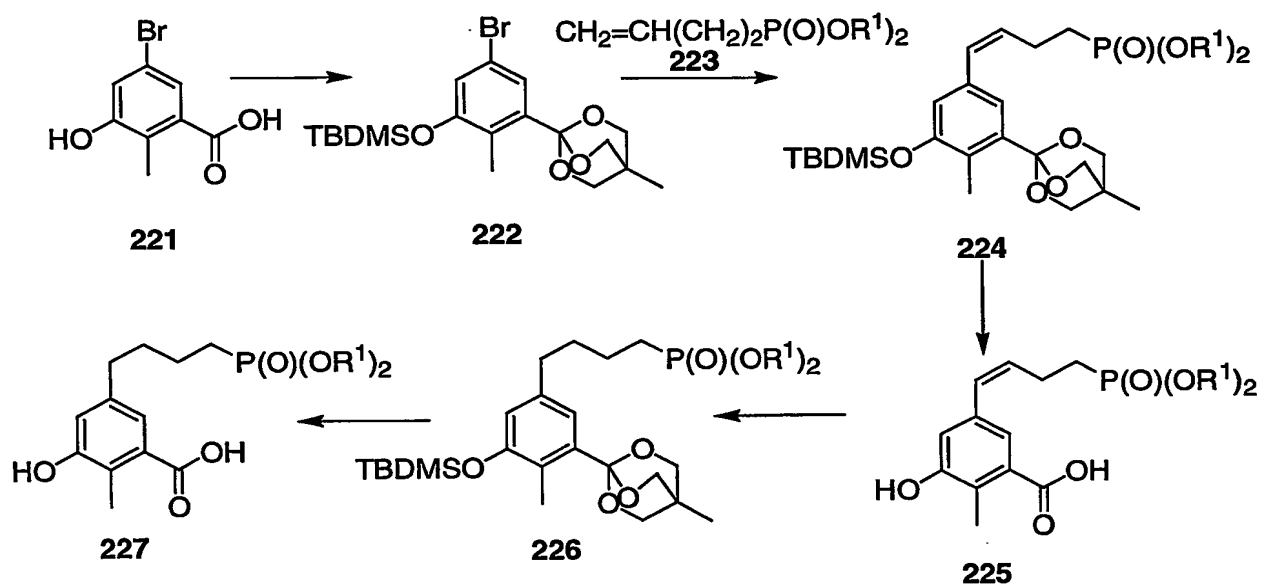
Example



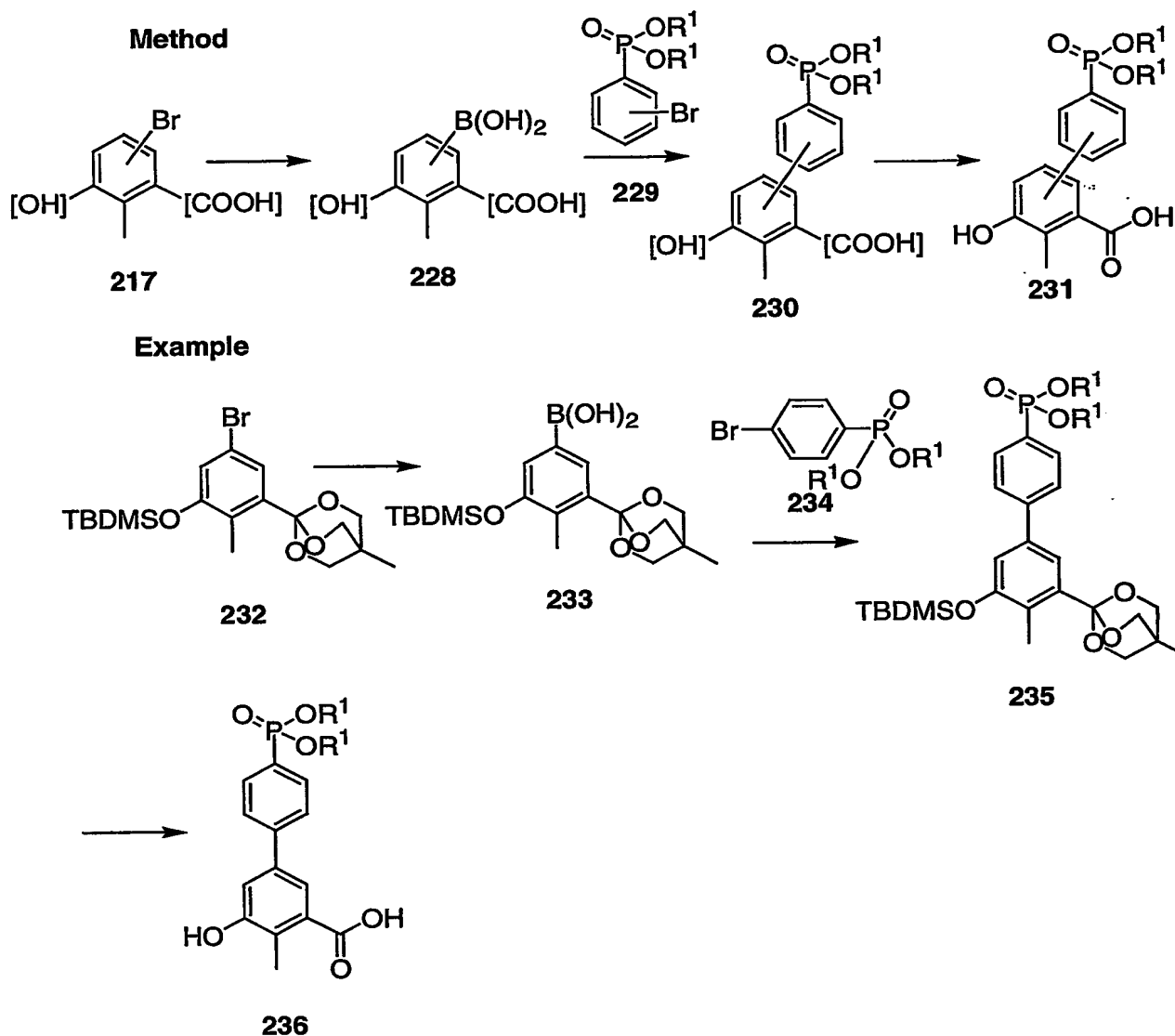
Scheme 34
Method



Example



Scheme 35



Preparation of tert-butylamine derivatives incorporating phosphonate moieties.

- 5 Scheme 36 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethylbromide **237** is reacted with a trialkyl phosphite, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **238**.

For example, the cbz derivative of 2,2-dimethyl-2-aminoethylbromide **240**, is heated with a trialkyl phosphite at ca 150° to afford the product **241**. Deprotection, as previously described, then affords the free amine **242**.

Using the above procedures, but employing different trisubstituted phosphites, there are
5 obtained the corresponding amines **239**.

Scheme **37** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain.

An optionally protected alcohol or thiol **243** is reacted with a bromoalkylphosphonate **146**, to
10 afford the displacement product **244**. Deprotection, if needed, then yields the amine **245**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **246** is reacted with a dialkyl 4-bromobutyl phosphonate **247**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and potassium iodide, at ca 60° to afford the phosphonate **248**. Deprotection then affords the free amine **249**.

15 Using the above procedures, but employing different alcohols or thiols **243**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **245**.

Scheme **38** describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

20 In the procedure, a terminal acetylenic derivative of tert-butylamine **250** is reacted, under basic conditions, with a dialkyl chlorophosphite **115**, as described above in the preparation of **104**, (Scheme **21**). The coupled product **251** is deprotected to afford the amine **252**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **253** and **254** respectively.

25 For example, 2-amino-2-methylprop-1-yne **255**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **256**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite
30 **115** to afford the phosphonate **257**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **258**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for

Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **259**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **260**.

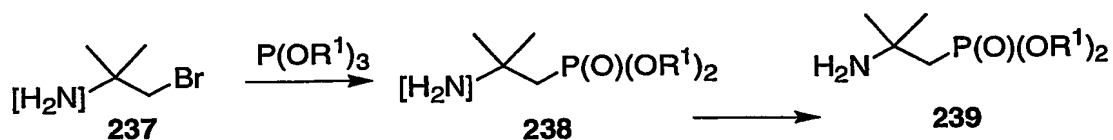
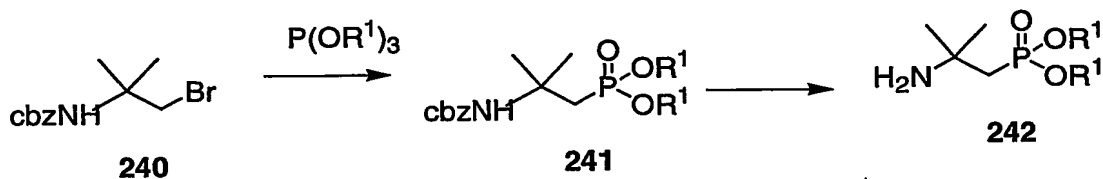
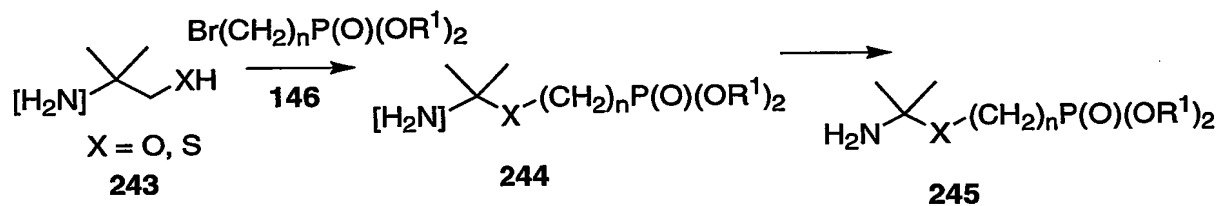
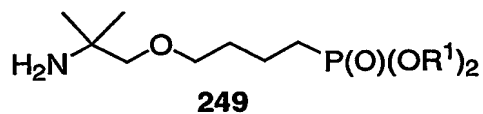
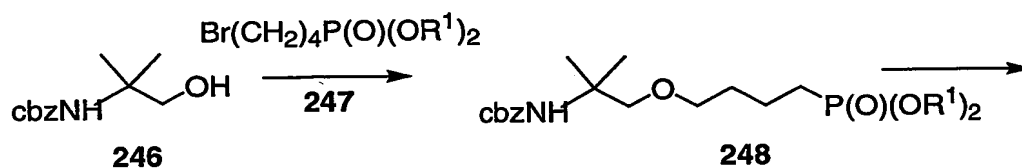
- 5 Using the above procedures, but employing different acetylenic amines **250**, there are obtained the corresponding products **252**, **253** and **254**.

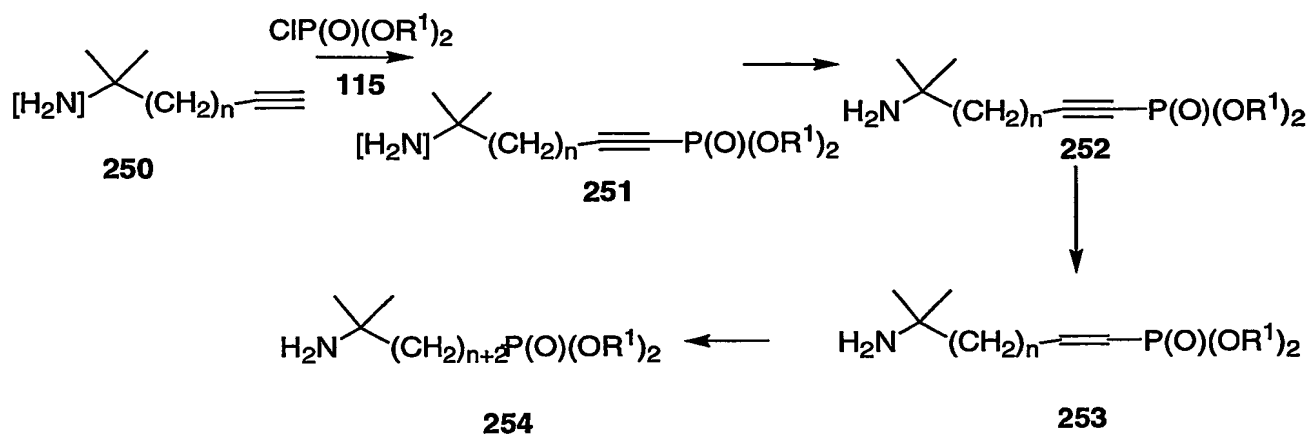
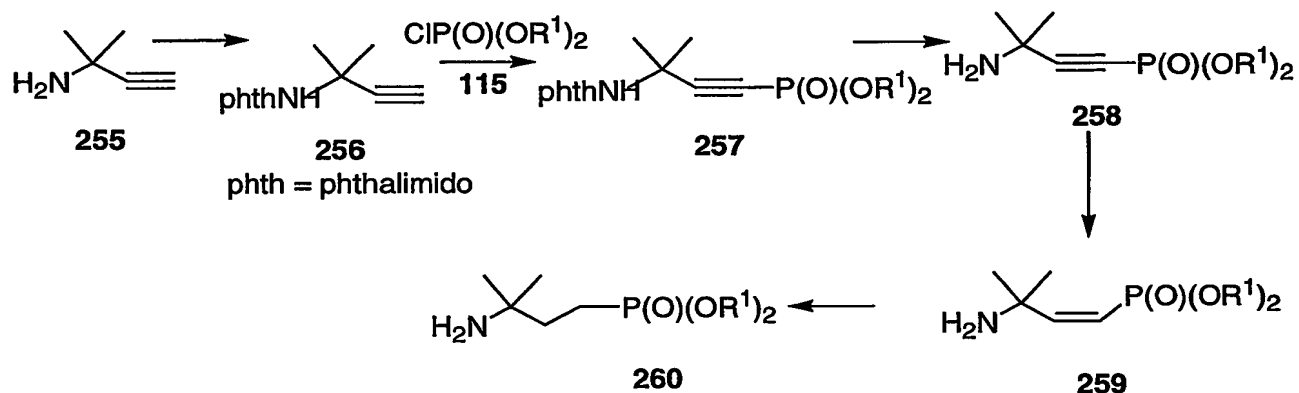
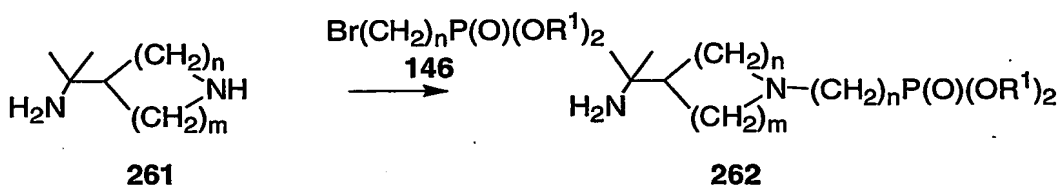
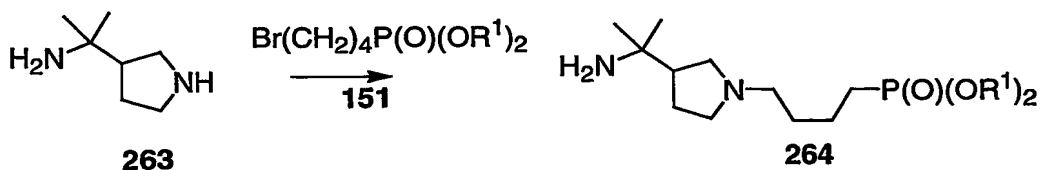
Scheme 39 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

- 10 In this method, an aminoethyl-substituted cyclic amine **261** is reacted with a limited amount of a bromoalkyl phosphonate **146**, using, for example, the conditions described above for the preparation of **147**, (Scheme 25) to afford the displacement product **262**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **263**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate

- 15 **151**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **264**.
Using the above procedures, but employing different cyclic amines **261**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **262**.

Scheme 36**Method****Example****Scheme 37****Method****Example**

Scheme 38**Method****Example****Scheme 39****Method****Example**

Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Chart 6 illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate **265** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **266**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **267**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **267**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **268**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **268** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **265**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **265** can be obtained from 2-hydroxyphenylalanine **269**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **269** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **265**, in which R is H.

Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **270**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **265** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°, to afford the decahydroisoquinoline **270**.

Protection of the carboxyl and NH groups present in **270** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **276**, in which R is trichloroethyl and R₁ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol **277**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as, for example, isopropanol, at ambient temperature, to afford the alcohol **277**. The alcohol **270** carboxyl and NH groups can be protected, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and by conversion of the NH into the N-cbz group, as described above. The protected alcohol **270** can then be converted into the thiol **271** and the amine **272**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **270** can be converted into an activated ester, for example trifluoromethanesulfonyl ester or the methanesulfonate ester **273**, by treatment with methanesulfonyl chloride, as described above for the preparation of **63**, (Scheme 1). The mesylate **273** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **271**.

For example, the mesylate **273** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **274**, in which R₂ is COCH₃. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **271**.

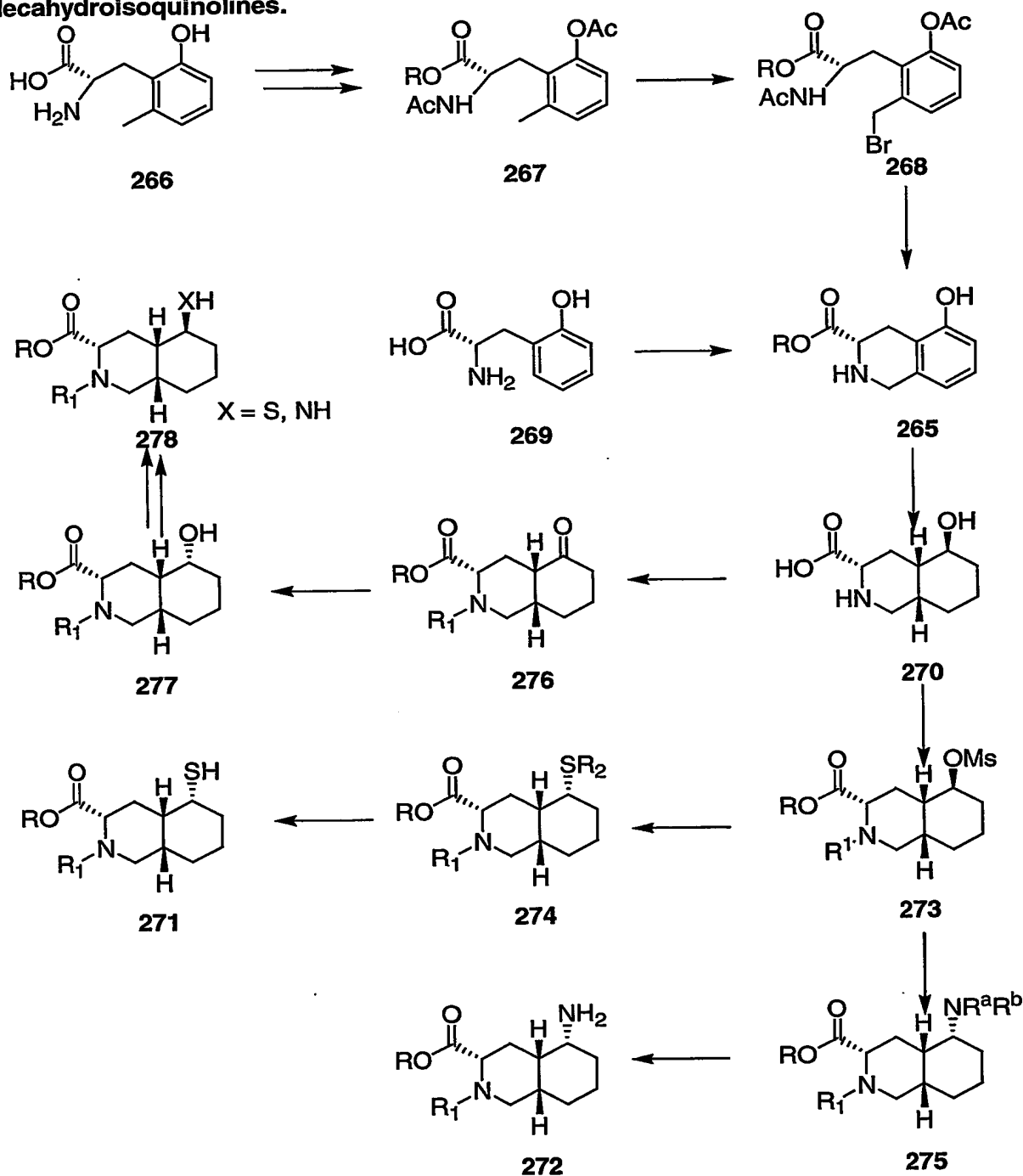
The mesylate **273** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, to afford the amine **272**.

For example, the mesylate **273** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **275**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example
5 by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **272**.

The application of the procedures described above for the conversion of the β -carbinol **270** to the α -thiol **271** and the α -amine **272** can also be applied to the α -carbinol **277**, so as to afford the β -thiol and β -amine, **278**.

10

Chart 6. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.



Scheme 40 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine **279** is reacted with a bromoalkyl phosphonate

5 **146**, under the conditions described above for the preparation of **147** (Scheme 25), to afford

the displacement product **280**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **281**.

For example, the compound **282**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **283**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **284**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **285**.

Using the above procedures, but employing, in place of the α -thiol **282**, the alcohols, thiols or amines **270**, **272**, **277**, and **278**, of either α - or β -orientation, there are obtained the corresponding products **281**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 41 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **272** or **278** are reacted with a phosphonate aldehyde **286**, in the presence of a reducing agent, to afford the alkylated amine **287**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **288**.

For example, the protected amino compound **272** is reacted with a dialkyl formylphosphonate **289**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **290**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **291**.

Using the above procedures, but employing, instead of the α -amine **272**, the β isomer, **278** and/or different aldehydes **286**, there are obtained the corresponding products **288**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme 42 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate 292 is reacted with a mesylate 293, to effect

- 5 displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product 294. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 295. For example, the protected mesylate 273 is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate 296, the preparation of which is described in Aust. J. Chem., 43, 10 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate 297. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 298.
- 15 Using the above procedures, but employing, instead of the phosphonate 296, different phosphonates 292, there are obtained the corresponding products 295.

- Scheme 43 illustrates the preparation of decahydroisoquinoline phosphonates 299 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds 20 are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 300 and a bromomethyl substituted phosphonate 301. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 300. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or 25 lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds 302. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 299.

- For example, the protected alcohol 303 is reacted at ambient temperature with a dialkyl 3- 30 bromomethyl phenylmethylphosphonate 304, the preparation of which is described above, (Scheme 29). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a

strong base, such as, for example, lithium hexamethyldisylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **304**, to afford the product **305**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **306**.

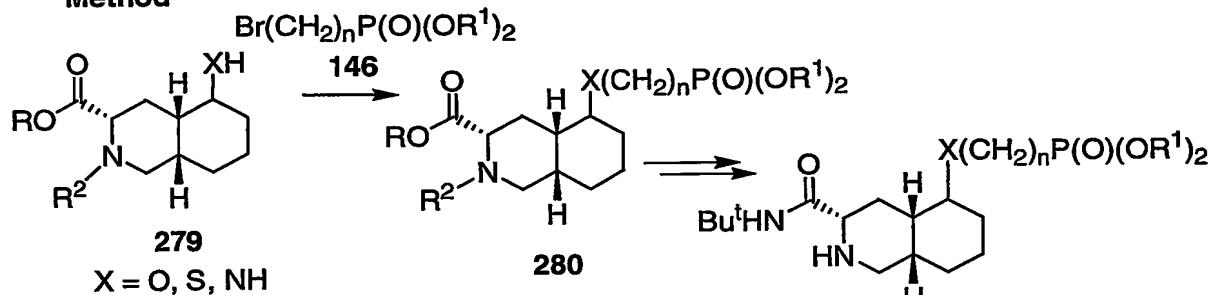
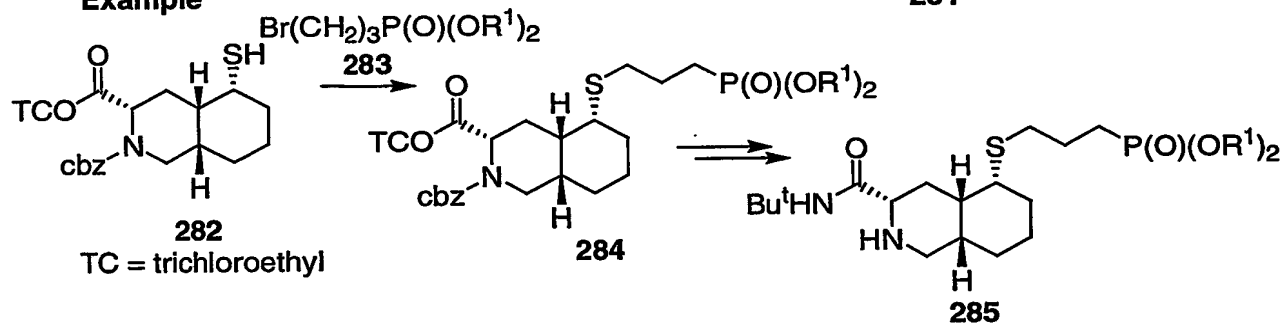
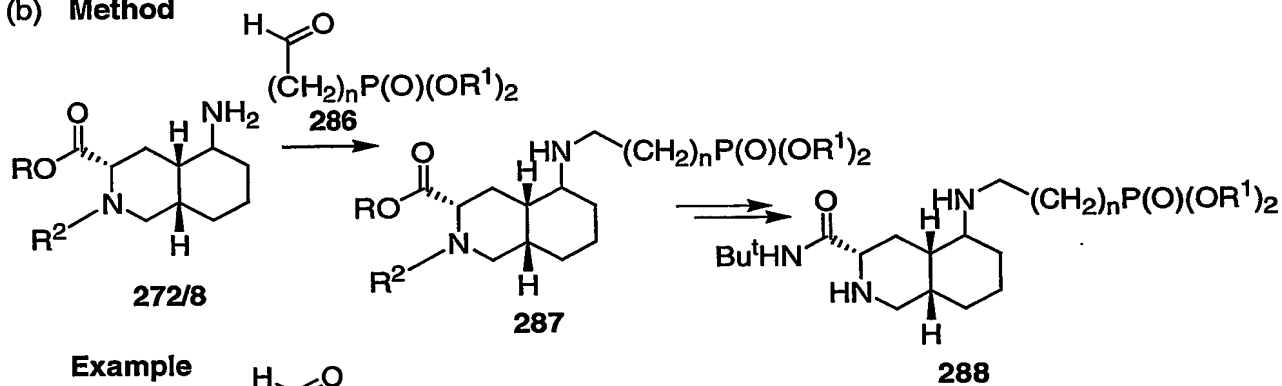
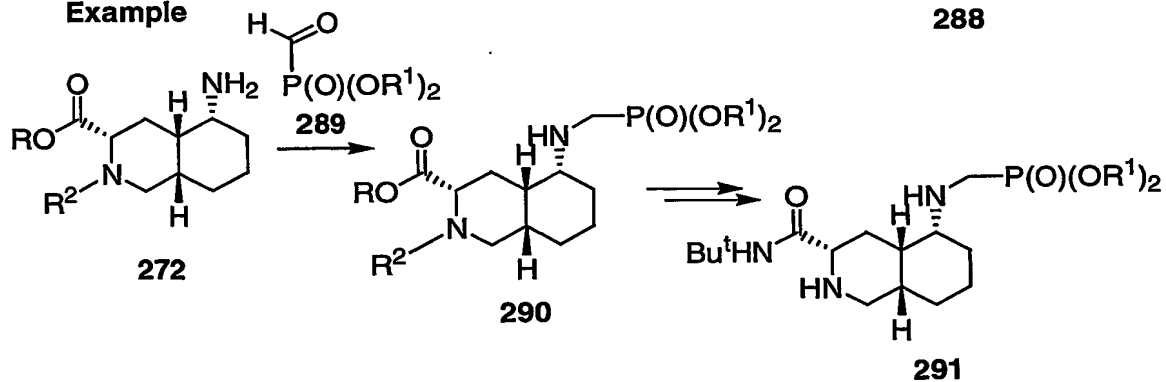
5 Using the above procedures, but employing, instead of the β -carbinol **303**, different carbinols, thiols or amines **300**, of either α - or β -orientation, and/or different phosphonates **301**, in place of the phosphonate **304**, there are obtained the corresponding products **299**, in which the orientation of the side-chain is the same as that of the starting material **300**.

10 Schemes **43-43** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **44** illustrates the conversion of the latter group of compounds **307** (in which the group B is link-P(O)(OR¹)₂ and precursor compounds thereto (in which B is an optionally protected precursor to the group link-P(O)(OR¹)₂ such as, for example, OH, SH, NH₂) to the
15 corresponding tert butyl amides **88**.

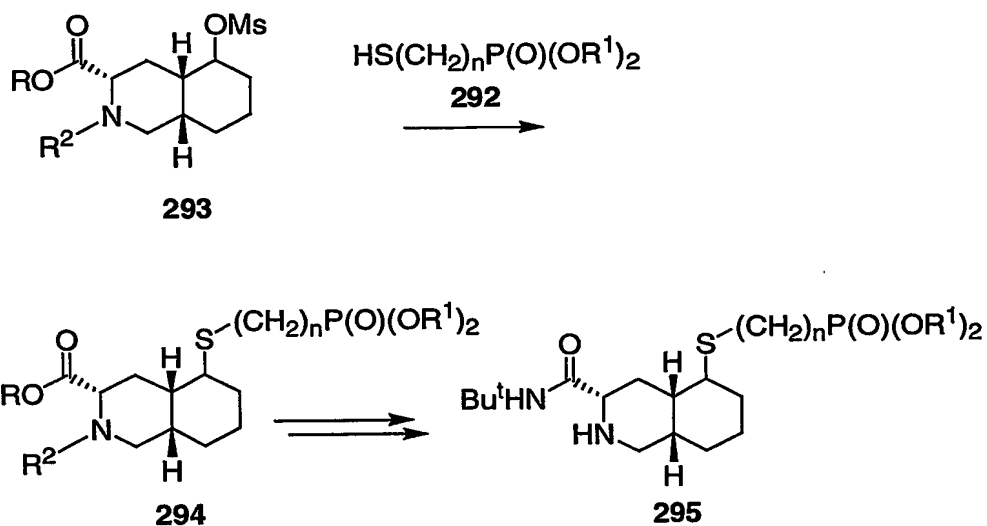
As shown in Scheme **44**, the ester compounds **307** are deprotected to form the corresponding carboxylic acids **308**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is
20 removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **308** to the tert. butyl amide **309** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with tert. butylamine, as described above for the preparation of **62** (Scheme **1**). Deprotection of the NR² group, as described above, then affords the free amine **88**.

25

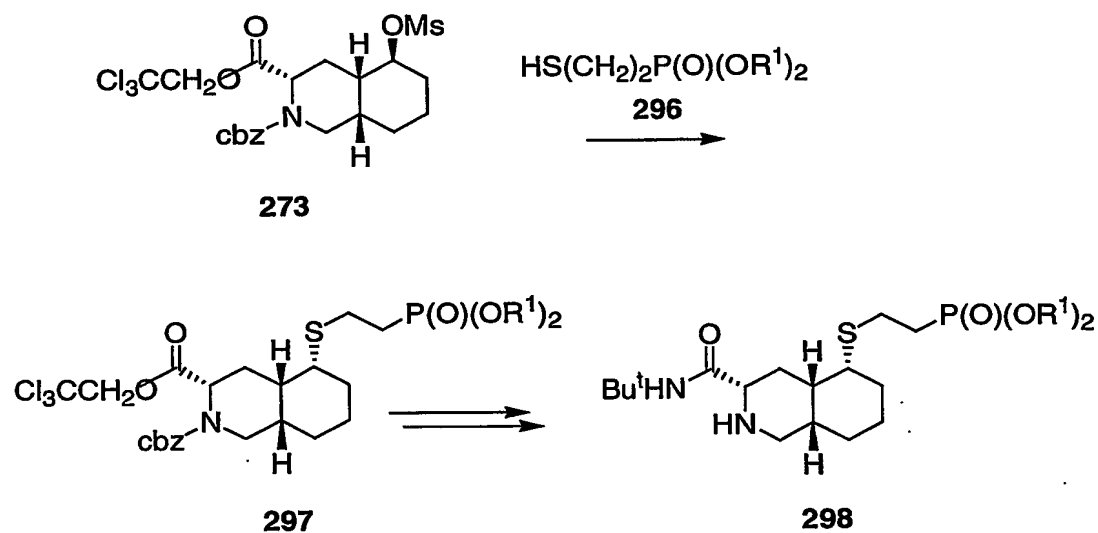
Scheme 40**Method****Example****Scheme 41****(b) Method****Example**

Scheme 42

Method

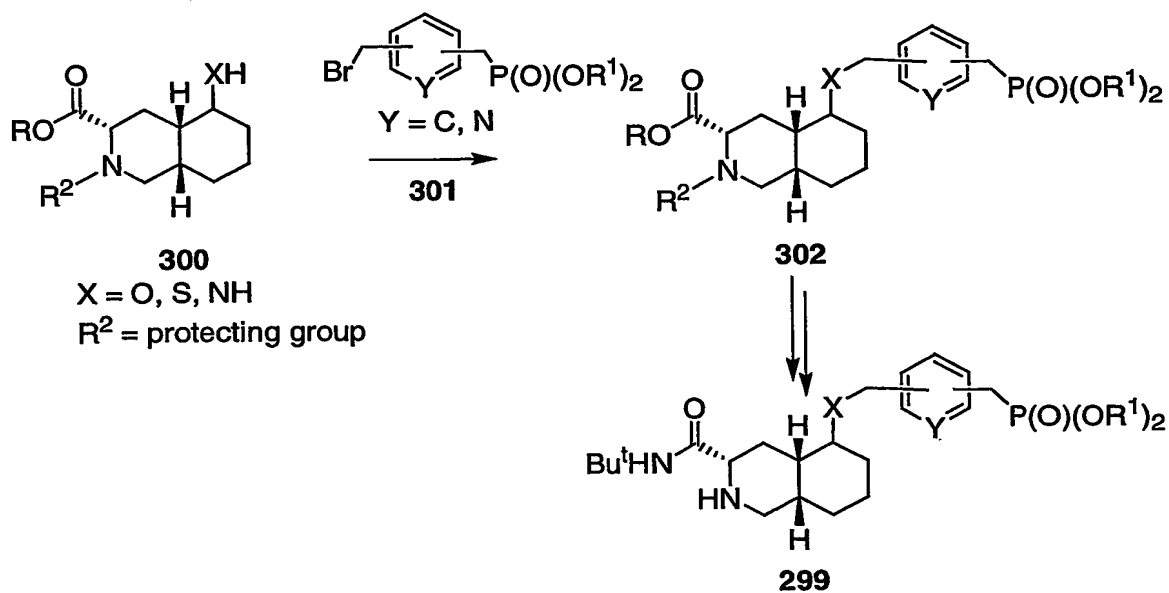


Example

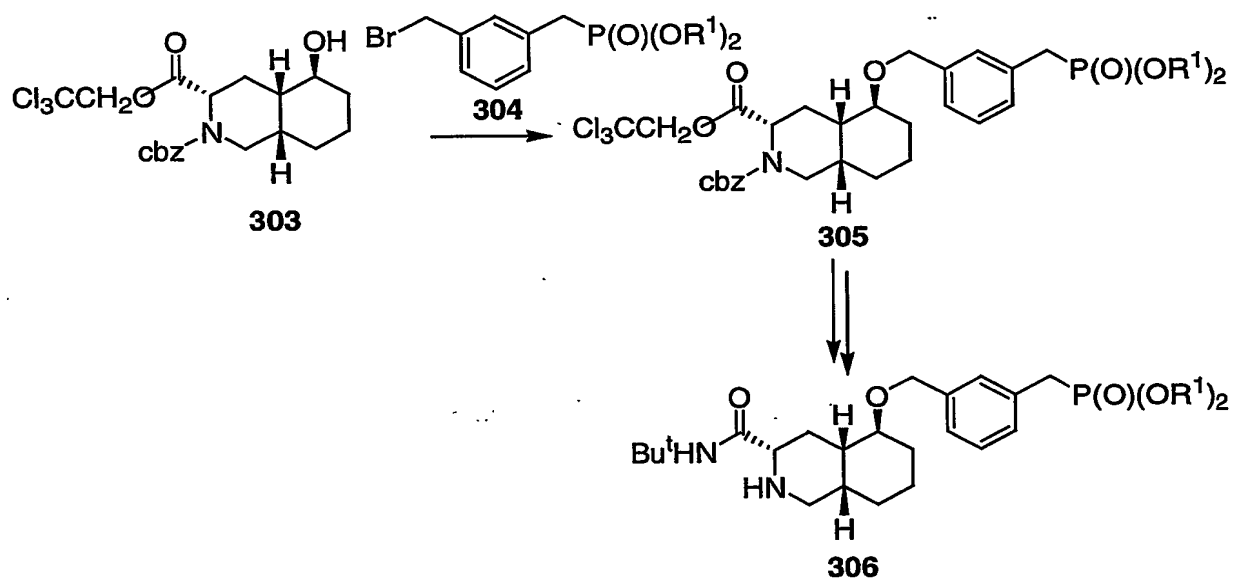


Scheme 43

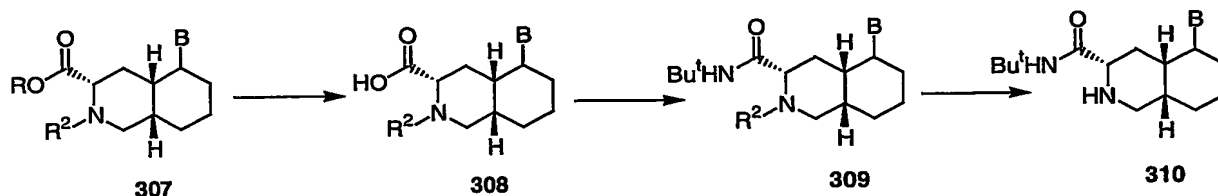
Method



Example



Scheme 44



Preparation of phenylalanine derivatives incorporating phosphonate moieties.

Scheme 45 illustrates the conversion of variously substituted phenylalanine derivatives **311**

5 into epoxides **14a-1**, the incorporation of which into the compounds **2** is depicted in Scheme **14a**.

A number of compounds **311** or **312**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds **311** or **312** are described in the literature. For example, the preparation of compounds **311** or **312** in which X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Amer. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds **311**, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

15 The variously substituted aminoacids **312** are protected, for example by conversion to the BOC derivative **313**, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product **313** is then converted into the methyl ester **314**, for example by treatment with ethereal diazomethane. The substituent X in **314** is then transformed, using the methods described below, Schemes 46-48, into the group A. The products **315** are then

20 converted, via the intermediates **316-319**, into the epoxides **14a-1**. The methyl ester **315** is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid **316**. The conversion of the carboxylic acid **316** into the epoxide **14a-1**, for example using the sequence of reactions which is described in J. Med. Chem., 1994,

25 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **317**. The diazoketone is converted into

the chloroketone **318** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **319** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **14a-1**. Optionally, the above described series of reactions can be performed on the methyl ester **314**, so as to yield the epoxide **14a-1** in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds **314**, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes **46-48**.

Scheme **46** depicts the preparation of epoxides **322** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **314** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **320**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH₂OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **321**, which, employing the sequence of reactions shown in Scheme **45**, is transformed into the epoxide **322**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **323** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **138**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **324**. The latter compound is then converted, using the sequence of reactions shown in Scheme **45**, into the epoxide **325**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **314** in place of **323**, and/or different phosphonates **320**, the corresponding products **322** are obtained.

Scheme **47** illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative **314** is reacted with a dialkyl bromoalkyl phosphonate **146** to afford the product **326**. The conditions employed for this reaction are the same as those described above for the preparation of **148**, (Scheme 25) The product **326** is then transformed, using the sequence of reactions shown in Scheme 45, into the epoxide **327**.

For example, the protected aminoacid **328**, prepared as described above (Scheme 45) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate **329**, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product **330**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **331**.

Using the above procedures, but employing different phenols, thiols, and amines **314** in place of **328**, and/or different phosphonates **146**, the corresponding products **327** are obtained.

Scheme 48 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

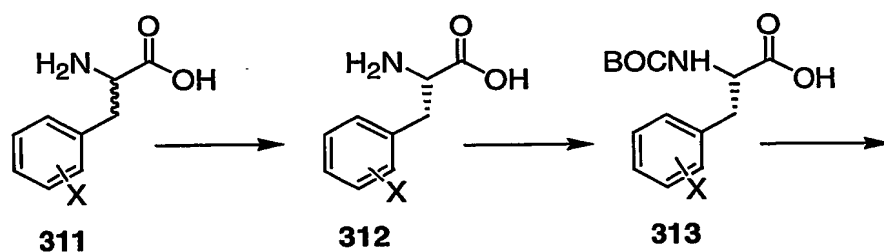
In this procedure, a protected hydroxymethyl-substituted phenylalanine **332** is converted into the halomethyl-substituted compound **333**. For example, the carbinol **332** is treated with triphenylphosphine and carbon tetrabromide, as described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product **333** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **334**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **335**, which, employing the sequence of reactions shown in Scheme 45, is transformed into the epoxide **336**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **337**, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **338**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **339**, the preparation of

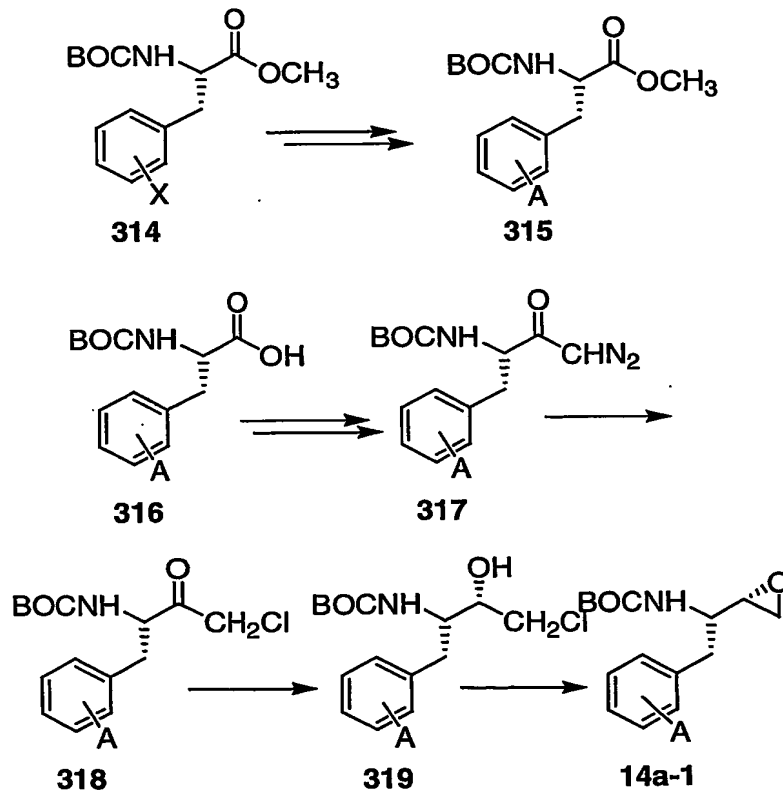
which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **340**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **341**.

- 5 Using the above procedures, but employing different carbinols **332** in place of **337**, and/or different phosphonates **334**, the corresponding products **336** are obtained.

Scheme 45

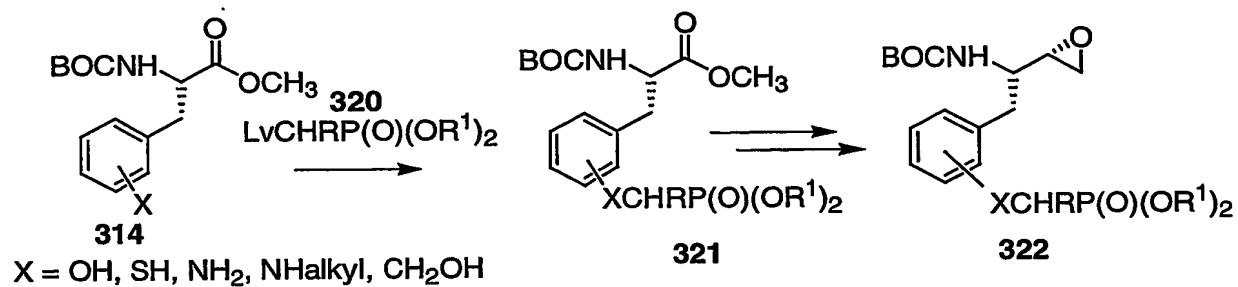


X = OH, SH, NH_2 , NHalkyl , CH_2OH

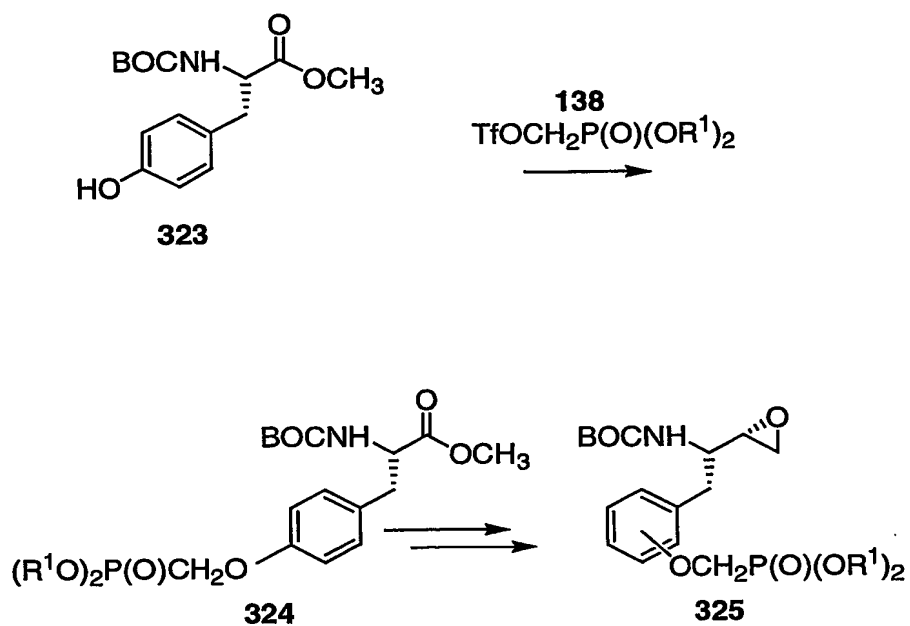


Scheme 46

Method

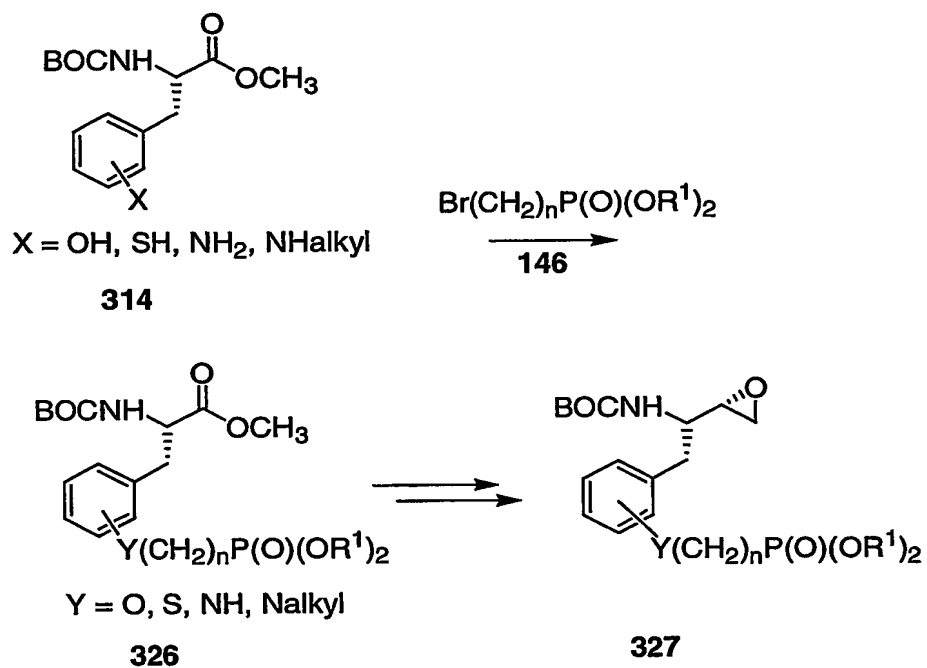


Example

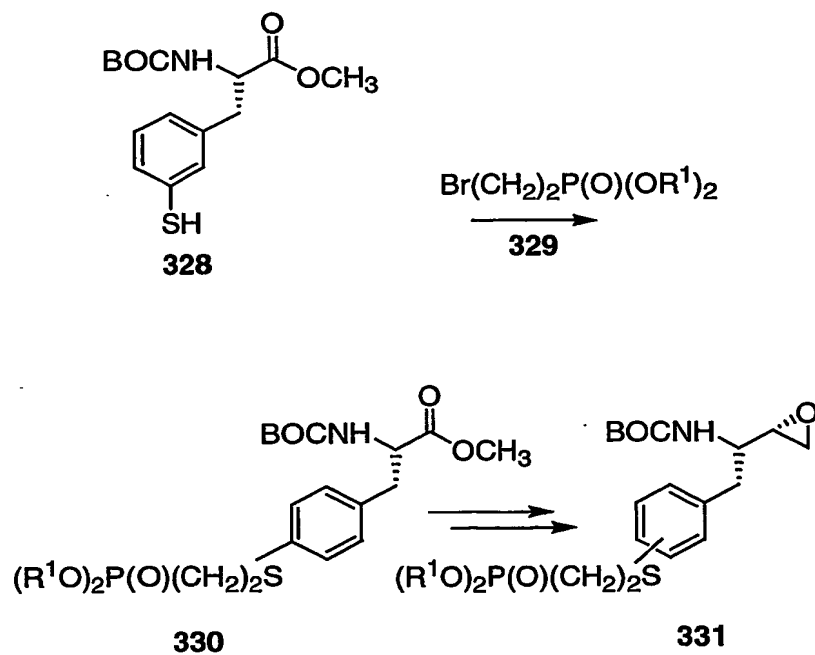


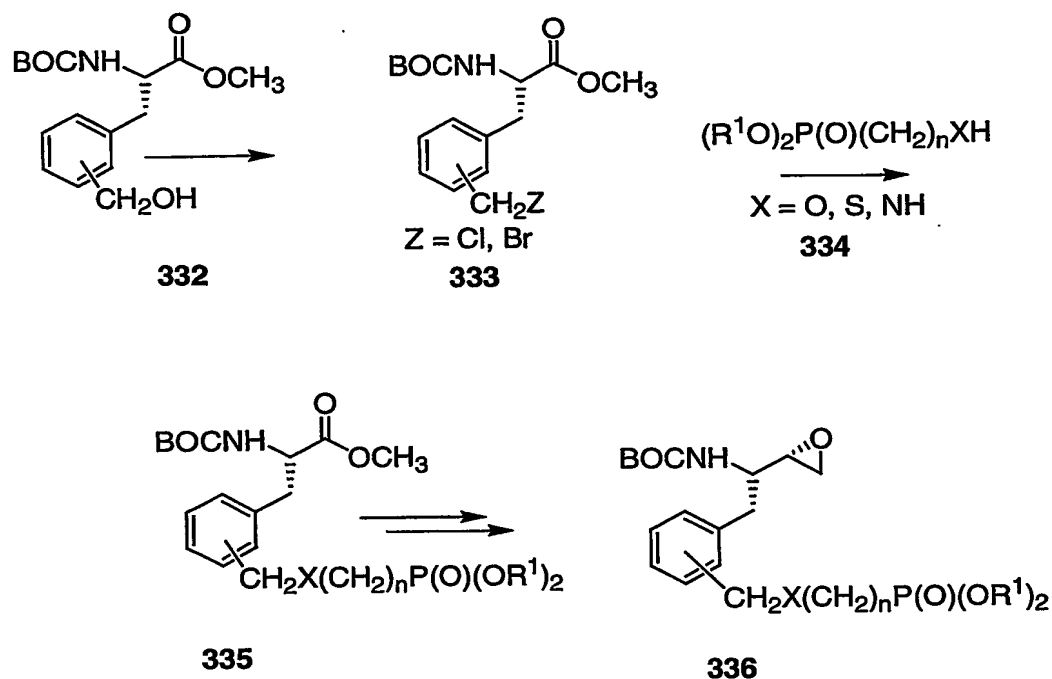
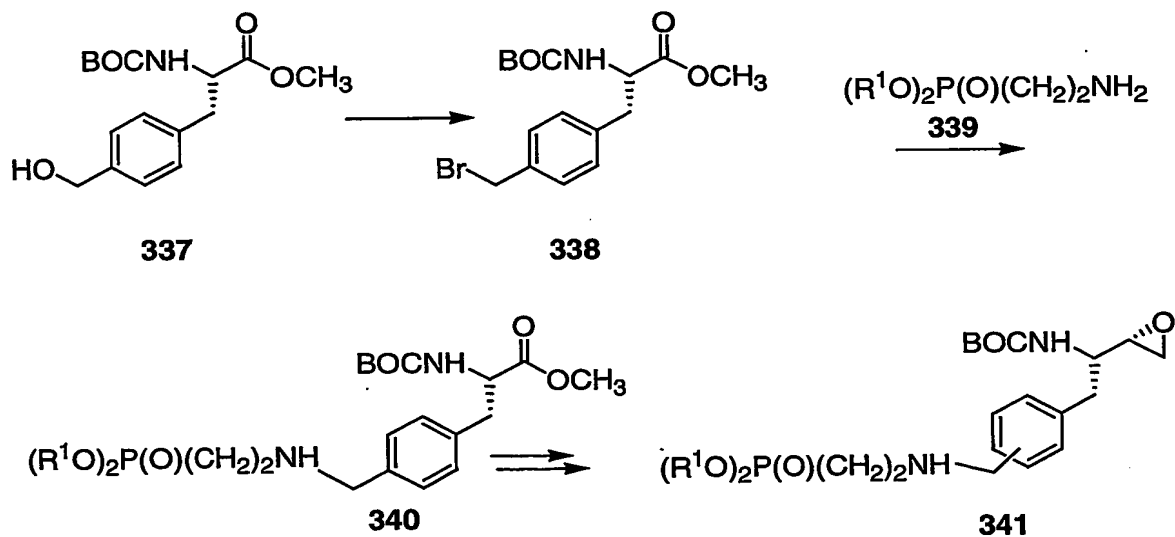
Scheme 47

Method



Example



Scheme 48**Method****Example**

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1-48 describe the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to phosphonate esters 1-4a, or to precursors thereto,

may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 49. The group R in Scheme 49 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-4a or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-4a. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 342 into the corresponding phosphonate monoester 343 (Scheme 49, Reaction 1) can be accomplished by a number of methods. For example, the ester 342 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 343 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 342 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 343 can be effected by treatment of the ester 342 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 343 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 343 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 343 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 342 or a phosphonate monoester 343 into the corresponding phosphonic acid 344 (Scheme 49, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 343

- in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **344** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **343** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **344** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.
- Palladium catalyzed hydrogenolysis of phosphonate esters **342** in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **342** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.
- 10 The conversion of a phosphonate monoester **343** into a phosphonate diester **342** (Scheme 49, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **343** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a
- 15 carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
- 20 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **342** to the diester **342** can be effected by the use of the Mitsunobu reaction, as described above (Scheme 16). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the
- 25 phosphonate monoester **343** can be transformed into the phosphonate diester **342**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the
- 30 phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **343** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M.

Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **342**.

5 A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme **49**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **342**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

10 A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ **344** can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **342** (Scheme **49**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **344** can be transformed into phosphonic esters **342** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **344** can be transformed into phosphonic
15 esters **342** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **342**.

20 Preparation of carbamates.

The phosphonate ester compounds **2-4a** in which the R^5CO group is derived from the carbonic acid derivatives **C38-C49**, the structures of which are shown in Chart **4c**, are carbamates. The compounds have the general structure $\text{ROCONHR}'$, wherein the
25 substructure ROCO represents the group R^5CO , as defined in Chart **4c**, and the substituent R' represents the substructure to which the amine group is attached. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
30 Scheme **50** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **50**, in the general reaction generating carbamates, a carbinol **345** is

converted into the activated derivative **346** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **346** is then reacted with an amine **347**, to afford the carbamate product **348**. Examples **1 – 7** in Scheme **50** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **50**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **349**. In this procedure, the carbinol **349** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **350**. The latter compound is then reacted with the amine component **347**, in the presence of an organic or inorganic base, to afford the carbamate **351**. For example, the chloroformyl compound **350** is reacted with the amine **347** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **351**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine..

Scheme **50**, Example 2 depicts the reaction of the chloroformate compound **350** with imidazole, **351**, to produce the imidazolide **352**. The imidazolide product is then reacted with the amine **347** to yield the carbamate **351**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **50** Example 3, depicts the reaction of the chloroformate **350** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **354**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **363 - 368** shown in Scheme **50**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **363**, N-hydroxysuccinimide **364**, or pentachlorophenol, **365**, the mixed carbonate **354** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **366** or 2-hydroxypyridine **367** can be performed in

an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 50 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 352 is employed. In this procedure, a carbinol 349 is reacted with an equimolar amount of carbonyl diimidazole 355 to prepare the intermediate 352. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 352 is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 351.

Scheme 50, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 357. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benzotriazole carbonyl chloride 356, to afford the alkoxy carbonyl product 357. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme 50, Example 6 illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, 358, is reacted with a carbinol 349 to afford the intermediate alkyloxycarbonyl intermediate 359. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The procedure in which the reagent 359 is derived from hydroxybenzotriazole 363 is described in Synthesis, 1993, 908; the procedure in which the reagent 359 is derived from N-hydroxysuccinimide 364 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 359 is derived from 2-hydroxypyridine 367 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 359 is derived from 4-nitrophenol 368 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 358 is conducted in an inert organic solvent at ambient temperature.

Scheme 50, Example 7 illustrates the preparation of carbamates from alkoxy carbonyl azides 360. In this procedure, an alkyl chloroformate 350 is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide 360. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is

conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 50, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure,

5 which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 351.

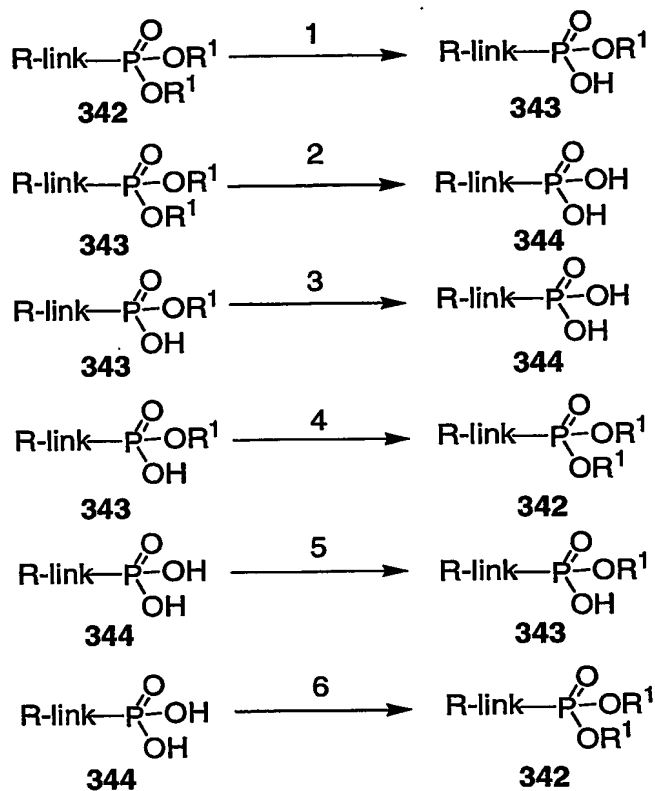
Scheme 50, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 362. In this procedure, which is described in

10 Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 351.

Scheme 50, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem.

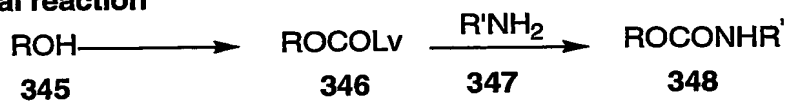
15 Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 351.

Scheme 49

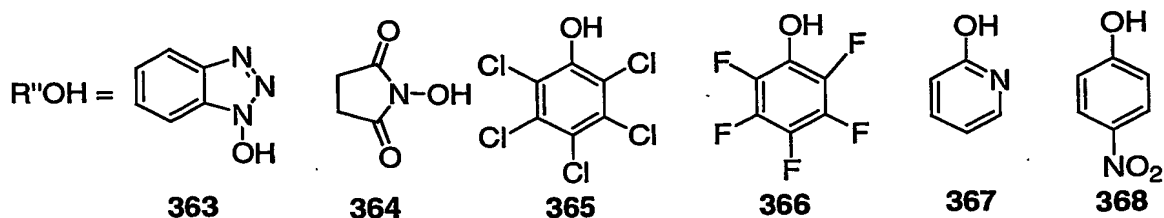
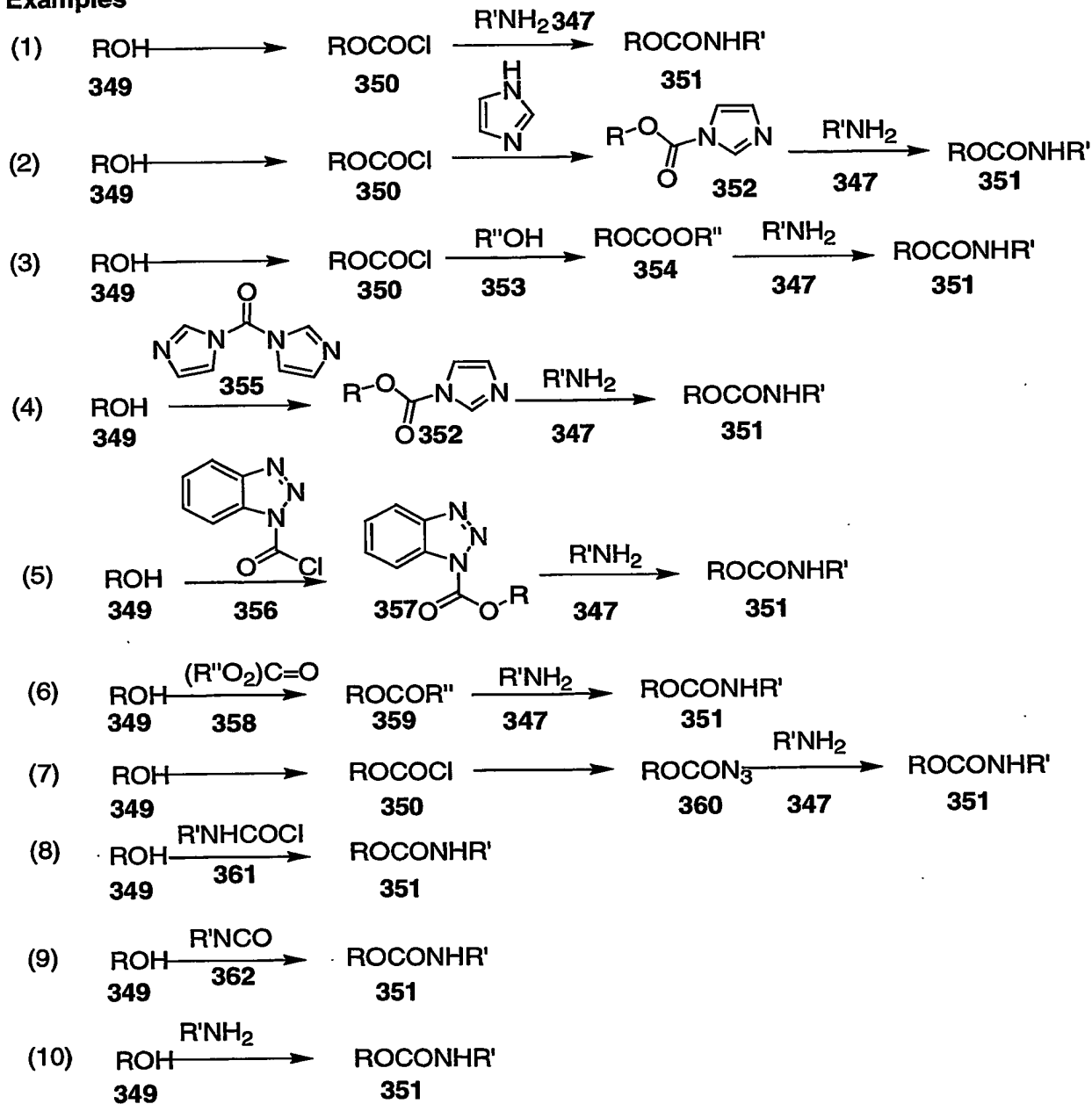


Scheme 50

General reaction



Examples



General applicability of methods for introduction of phosphonate substituents.

5 The above-described methods for the preparation of phosphonate-substituted thiols, Schemes 20 to 30, can, with appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines.

Similarly, preparative methods described above for phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines, Schemes 31 to 48, can, with
10 appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted thiophenols.

Preparation of compounds 1-4a with phosphonate moieties attached to any substructural component.

15 The chemical transformations described in Schemes 1-50 illustrate the preparation of compounds 1-4 in which the phosphonate ester moiety is attached to the hydroxymethyl benzoic acid group (Schemes 1-3), the phenylthio moiety (Schemes 4-6), the amine moiety (Schemes 7-9), the decahydroisoquinoline moiety (Schemes 10-12) and the phenyl moiety
20 (Schemes 10-14b).

Charts 2 - 4 illustrate various chemical substructures that may be substituted for the phosphonate-containing moieties. For example, in Chart 2, substructures 6, 7 and 8-20e may be substituted for the decahydroisoquinoline moiety, and in Chart 3, substructures 21-26 may be substituted for the group CH_2XR^4 in compounds 1-4. Charts 4a-c illustrate the structures
25 of the compounds R^5COOH which may be incorporated into the phosphonate esters 2-4. By utilization of the methods described herein for the preparation of, and incorporation of phosphonate-containing moieties, and by the application of the knowledge of one skilled in the art, the phosphonate ester moieties described herein may be incorporated into the amines 6, 7, and 8-20, into the R^4 groups 21-26, and into the carboxylic acids, or functional equivalents
30 thereof, with the structures C1-C49. Subsequently, the thus-obtained phosphonate-ester containing moieties may, utilizing the procedures described above in Schemes 1-14b, be incorporated into the compounds represented by the formula 4a (Chart 1) in which one of the

groups R^2NHCR^3 , R^4 , R^5 or Bu^t contains a phosphonate group of the general formula $link-P(O)(OR^1)_2$.

Lopinavir-like phosphonate protease inhibitors (LLPPI)

5

Preparation of the intermediate phosphonate esters.

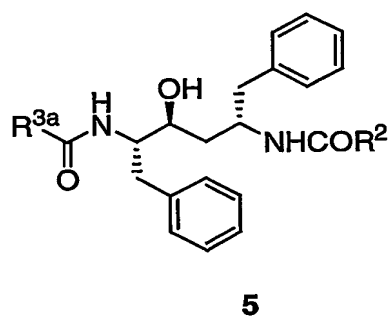
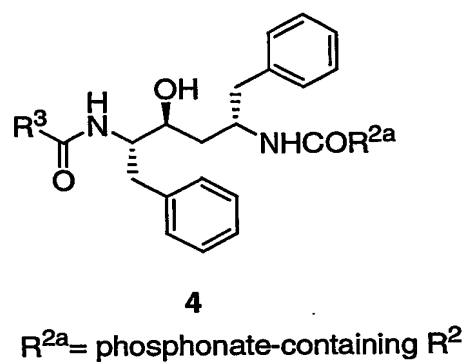
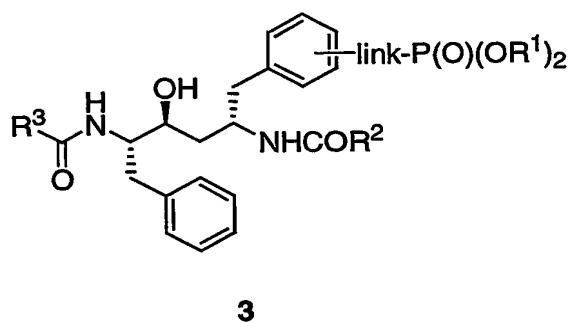
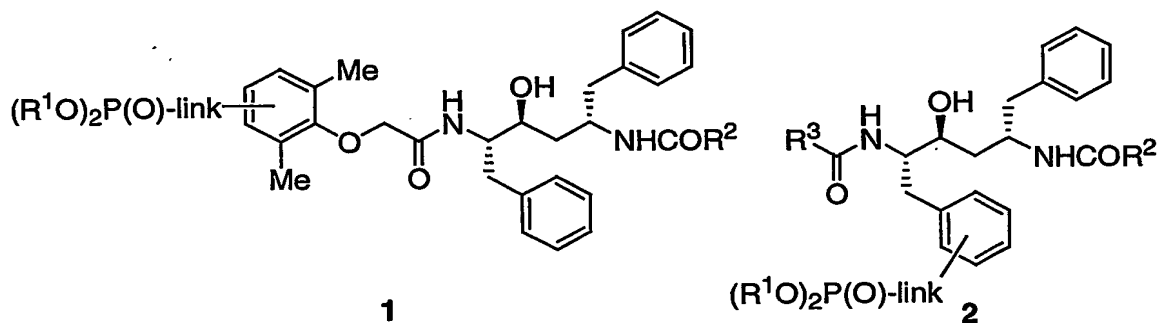
The structures of the intermediate phosphonate esters **1** to **5** and the structures for the component groups R^1 of this invention are shown in Chart 1.

10 The structures of the R^2COOH and R^3OOH components **C1- C49** are shown in Charts **2a**, **2b** and **2c**. Specific stereoisomers of some of the structures are shown in Charts **1**, and **2**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **5**. Subsequent chemical modifications to the compounds **1** to **5**, as described herein, permit the synthesis of the final compounds of this invention.

15 The intermediate compounds **1** to **5** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **4** and **5** illustrate examples of the linking groups present in the structures **1** – **5**, and in which "etc" refers to the scaffold, e.g., lopinavir.

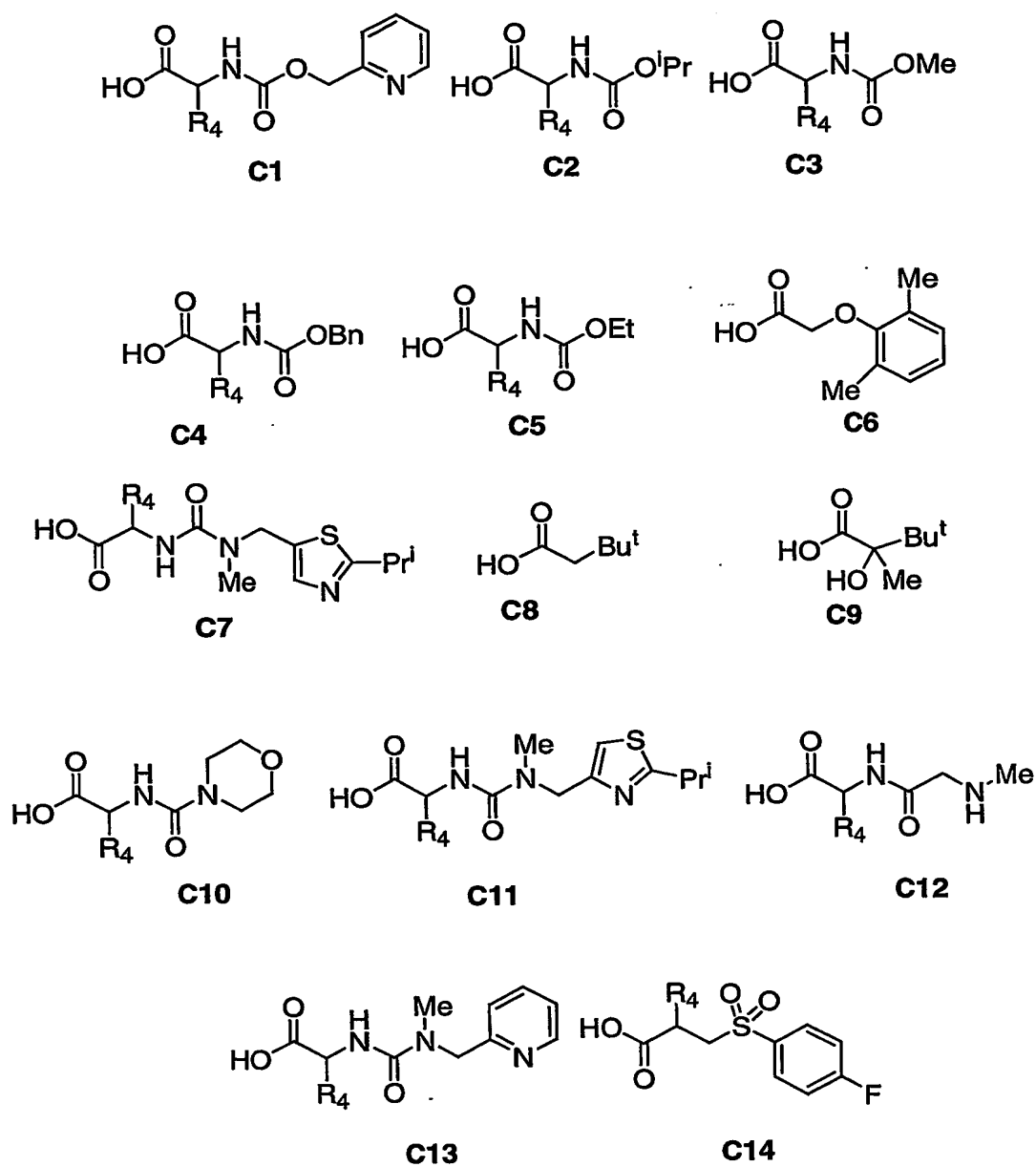
20 Schemes **1** - **33** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1- 3**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **4** and **5**, in which the phosphonate moiety is incorporated into different members of the groups R^2COOH and R^3COOH , is also described below.

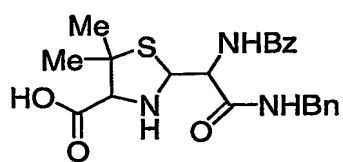
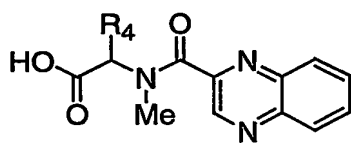
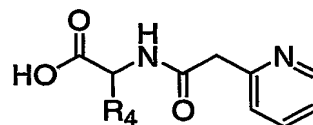
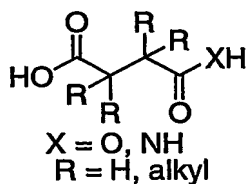
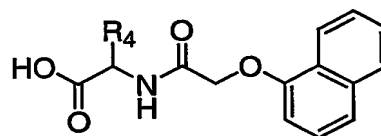
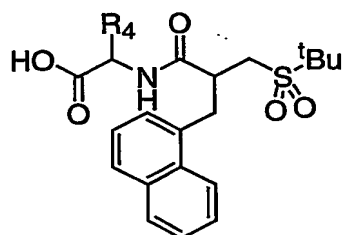
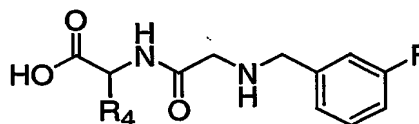
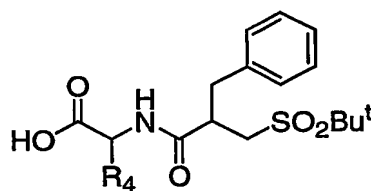
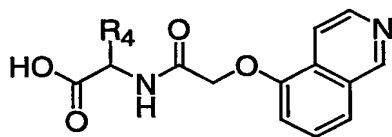
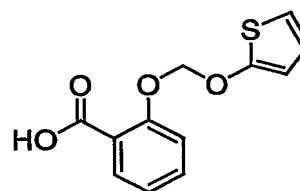
Chart 1 Intermediate phosphonate esters



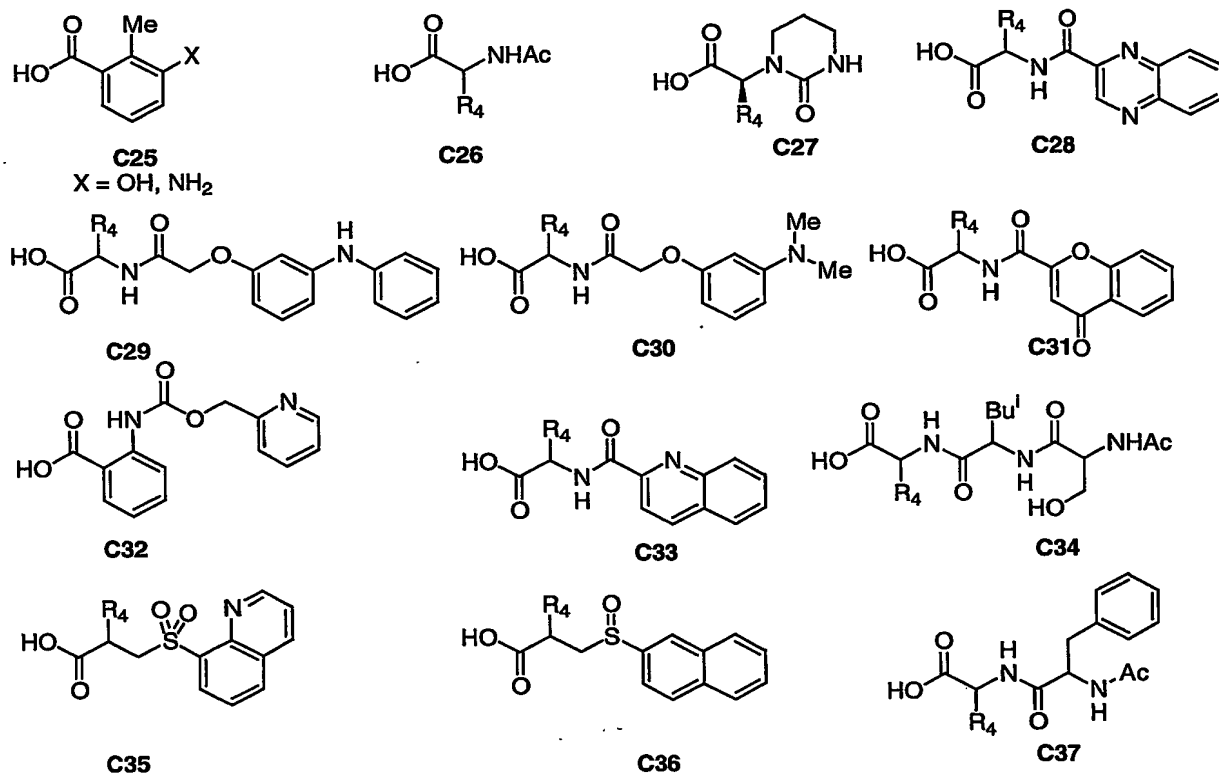
R^{3a} = phosphonate-containing R^3

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

Chart 2a Structures of the R²COOH and R³COOH components

**C15****C16****C17****C18****C19****C20****C21****C22****C23****C24**

R^4 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$

Chart 2b Structures of the R²COOH and R³COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

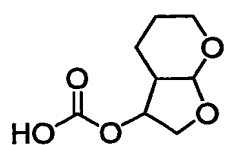
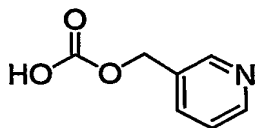
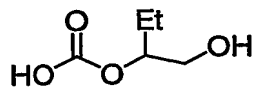
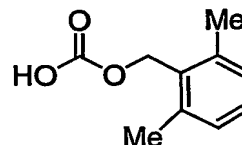
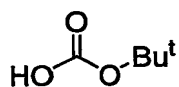
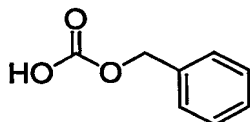
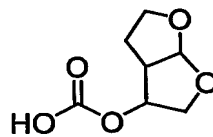
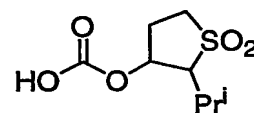
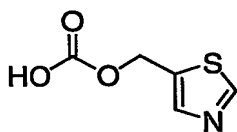
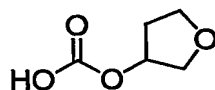
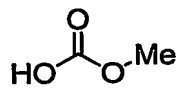
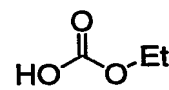
Chart 2c Structures of the R²COOH and R³COOH components**C38****C39****C40****C41****C42****C43****C44****C45****C46****C47****C48****C49**

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

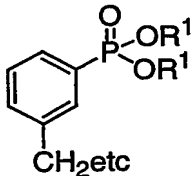
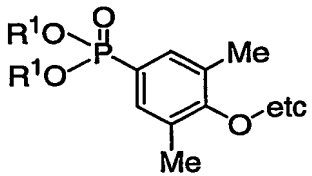
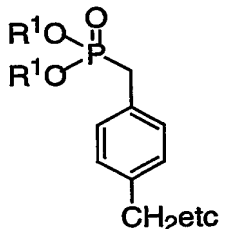
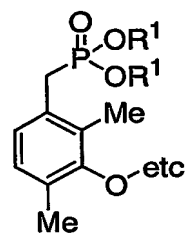
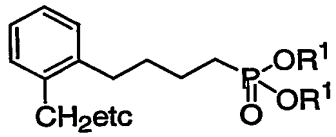
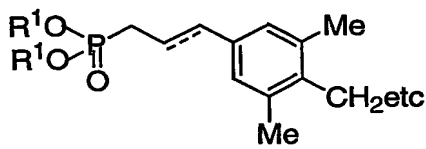
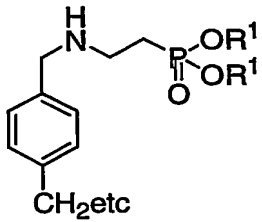
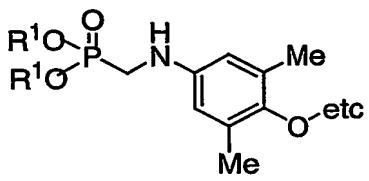
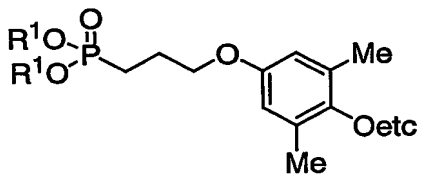
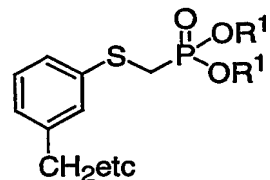
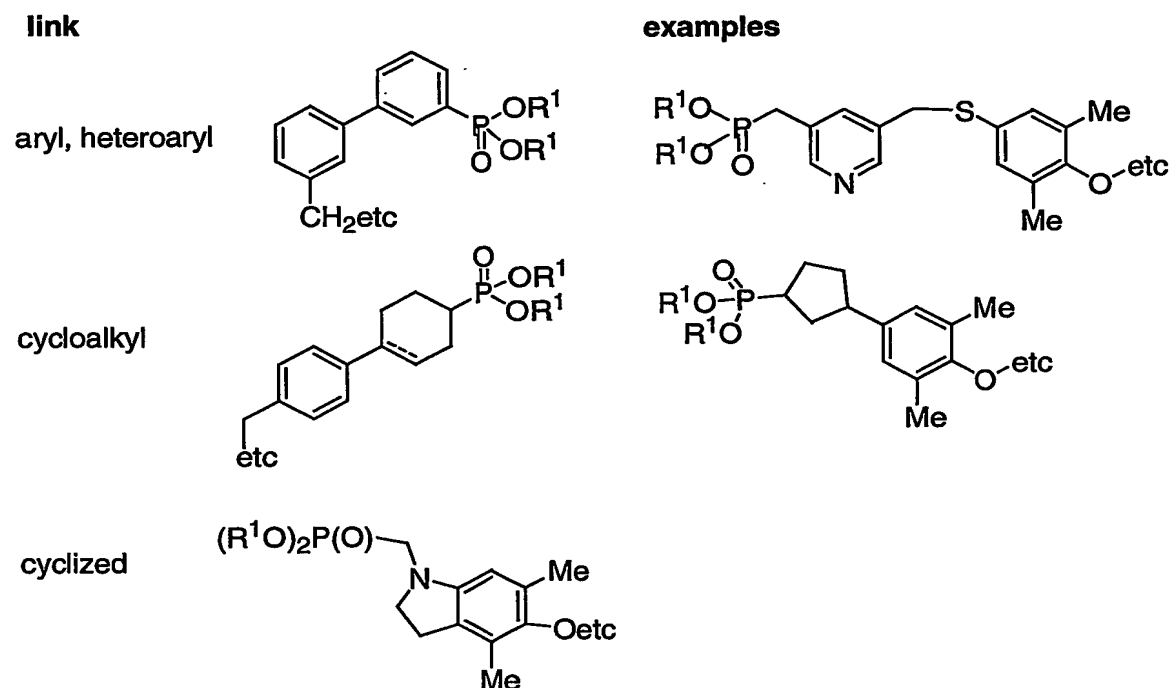
link	examples	
direct bond		
single carbon		
multiple carbon		
hetero atoms		
		

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.**Protection of reactive substituents.**

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

10

Preparation of the phosphonate intermediates 1.

15

Two methods for the preparation of the phosphonate intermediate compounds 1 are shown in Schemes 1 and 2. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 1, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH , or an activated derivative **1.2** thereof, to produce the amide **1.3**.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid is converted into the acid chloride **1.2**, $X = Cl$, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide product **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 365. The transformation can be effected under reductive conditions, for example by the use of hydrogen or a hydrogen transfer agent, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic

ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine **1.4** is then transformed into the amide **1.5** by reaction with the carboxylic acid **1.6**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH], [NH], [CHO], Br, as described below. Preparations of the carboxylic acids **1.6** are described below, Schemes 9-14. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**.

Preferably, the carboxylic acid **1.6** is converted into the acid chloride, and the acid chloride is reacted with the amine **1.4** in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product **1.5**.

Alternatively, the amide **1.5** can be obtained by the procedure shown in Scheme 2. In this method, 2-tert-butoxycarbonylamino-5-methyl-1,6-diphenyl-hexan-3-ol, **2.1**, the preparation of which is described in U.S. Patent 5,4912,53, is reacted with the carboxylic acid **1.6**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto. The reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

Preferably, equimolar amounts of the amine **2.1** and the carboxylic acid **1.6** are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide **2.2**.

The tert-butoxycarbonyl (BOC) protecting group is then removed from the product **2.2** to afford the free amine **2.3**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate **2.2** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,9142,32, to afford the free amine product **2.3**.

The amine product **2.3** is then reacted with the acid R^2COOH **2.4**, or an activated derivative thereof, to produce the amide **2.5**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

Preferably, equimolar amounts of the amine **2.3** and the carboxylic acid **2.4** are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide **1.5**.

The reactions illustrated in Schemes 1 and 2 illustrate the preparation of the compounds **1.5** in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 3 depicts the conversion of the compounds **1.5** in which A is OH, SH, NH, as described below, into the compounds **1** in which A is the group $link-P(O)(OR^1)_2$. In this procedure, the compounds **1.5** are converted, using the procedures described below, Schemes 9-33, into the compounds **1**.

Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds **2** are shown in Schemes 4 and 5. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme 4, the tribenzylated phenylalanine derivative **4.1**, in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion **4.2** derived from acetonitrile, to afford the ketonitrile **4.3**. Preparations of the tribenzylated phenylalanine derivatives **4.1** are described below, Schemes 15-17.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion **4.2**, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester **4.1** at low temperature, to afford the coupled product **4.3**.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40° , is added to a solution of one molar equivalent of the ester **4.1** in tetrahydrofuran at -40° , as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile **4.3**.

5 The above-described ketonitrile compound **4.3** is then reacted with an organometallic benzyl reagent, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine **4.5**. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80° to ambient temperature, to yield the benzylated product **4.5**.

10 Preferably, the ketonitrile **4.3** is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **4.5**.

The ketoenamine **4.5** is then reduced, in two stages, via the ketoamine **4.6**, to produce the
15 amino alcohol **4.7**. The transformation of the compound **4.5** to the aminoalcohol **4.7** can be effected in one step, or in two steps, with or without isolation of the intermediate ketoamine **4.6**, as described in U.S. Patent 5,491,253.

For example, the ketoenamine **4.5** is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as
20 methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine **4.6**. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The product **4.6** is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol **4.7**.

Alternatively, the ketoenamine **4.5** can be reduced to the aminoalcohol **4.7** without isolation of
25 the intermediate ketoamine **4.6**. In this procedure, as described in U.S. Patent 5,491,253, the ketoenamine **4.5** is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethylformamide or dimethylacetamide or the
30 like, to afford the aminoalcohol **4.7**.

The aminoalcohol **4.7** is converted into the amide **4.8** by reaction with the acid R^2COOH **2.4** or an activated derivative thereof, to produce the amide **4.8**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

The dibenzylated amide product **4.8** is then deprotected to afford the free amine **4.9**. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine **1.3** to yield the amine **1.4**, (Scheme 1).

The amine **4.9** is then reacted with the carboxylic acid R^3COOH (**4.10**) as defined in Charts **2a**–**2c**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

Alternatively, the amide **4.11** can be prepared by means of the sequence of reactions illustrated in Scheme 5.

In this sequence, the tribenzylated amino acid derivative **4.1** is converted, by means of the reaction sequence shown in Scheme 4, into the dibenzylated amine **4.7**. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative **5.1**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine **4.7** is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 59143332, to yield the BOC-protected product **5.1**.

The N-benzyl protecting groups are then removed from the amide product **5.1** to afford the free amine **5.2**. The conditions for this transformation are similar to those described above for the preparation of the amine **1.4**, (Scheme 1).

Preferably, the N, N-dibenzyl compound **5.1** is converted into the amine **5.2** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in US Patent 5914332

The amine compound **5.2** is then reacted with the carboxylic acid R^3COOH , or an activated derivative thereof, to produce the amide **5.3**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**, (Scheme 1).

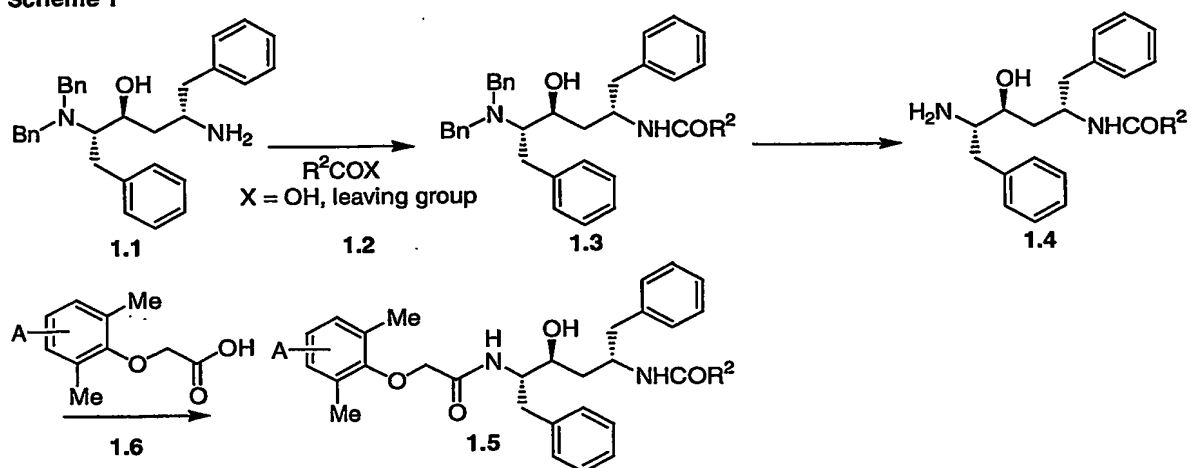
The BOC-protected amide **5.3** is then converted into the amine **5.4** by removal of the BOC protecting group. The conditions for this transformation are similar to those described above for the preparation of the amine **2.3** (Scheme 2). The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate **5.3** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in US Patent 5914232, to afford the free amine product **5.4**.

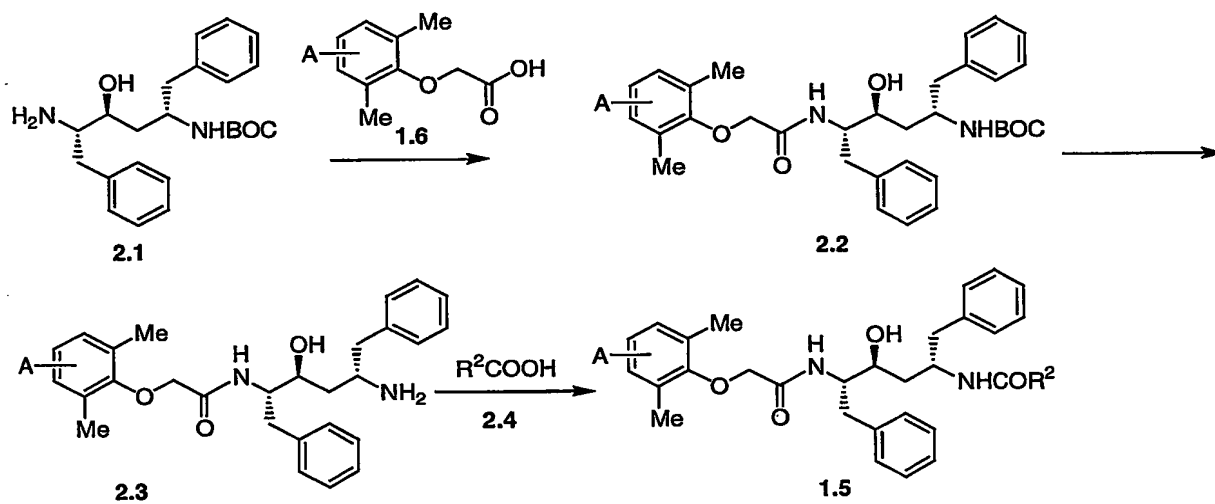
The free amine thus obtained is then reacted with the carboxylic acid R^2COOH **2.4**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

The reactions shown in Schemes 4 and 5 illustrate the preparation of the compounds **4.11** in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 6 depicts the conversion of the compounds **4.11** in which A is OH, SH, NH, as described below, into the compounds **2**. In this procedure, the compounds **4.11** are converted, using the procedures described below, Schemes 9-33, into the compounds **2**.

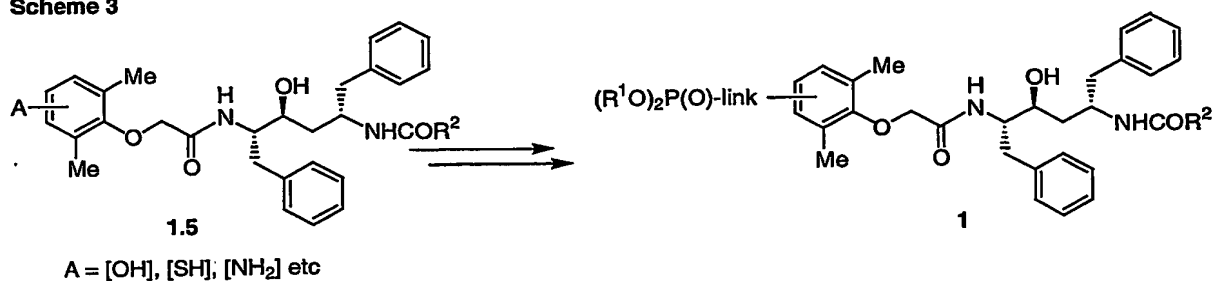
Scheme 1



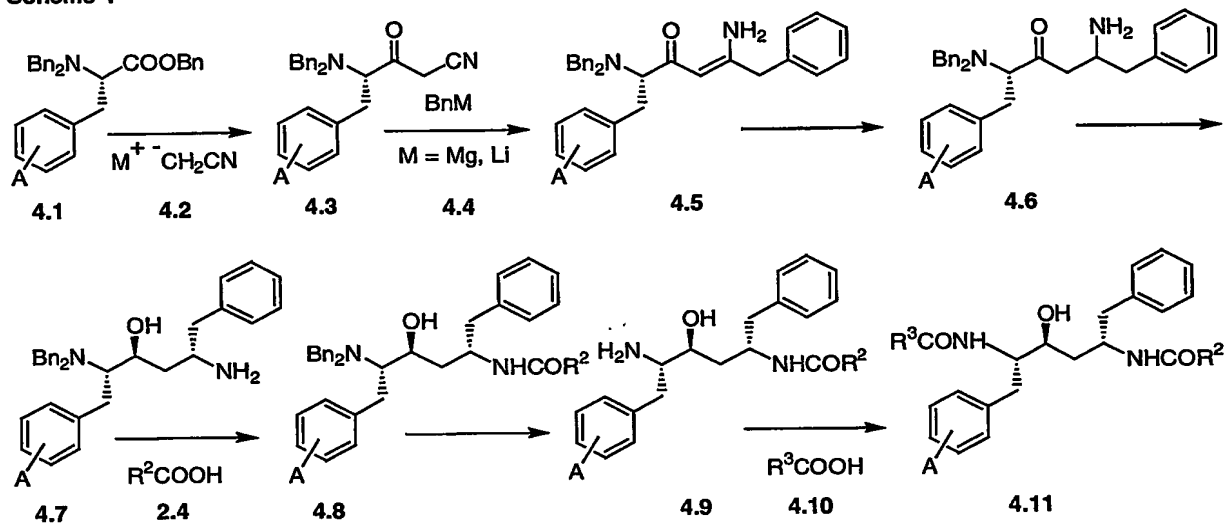
Scheme 2



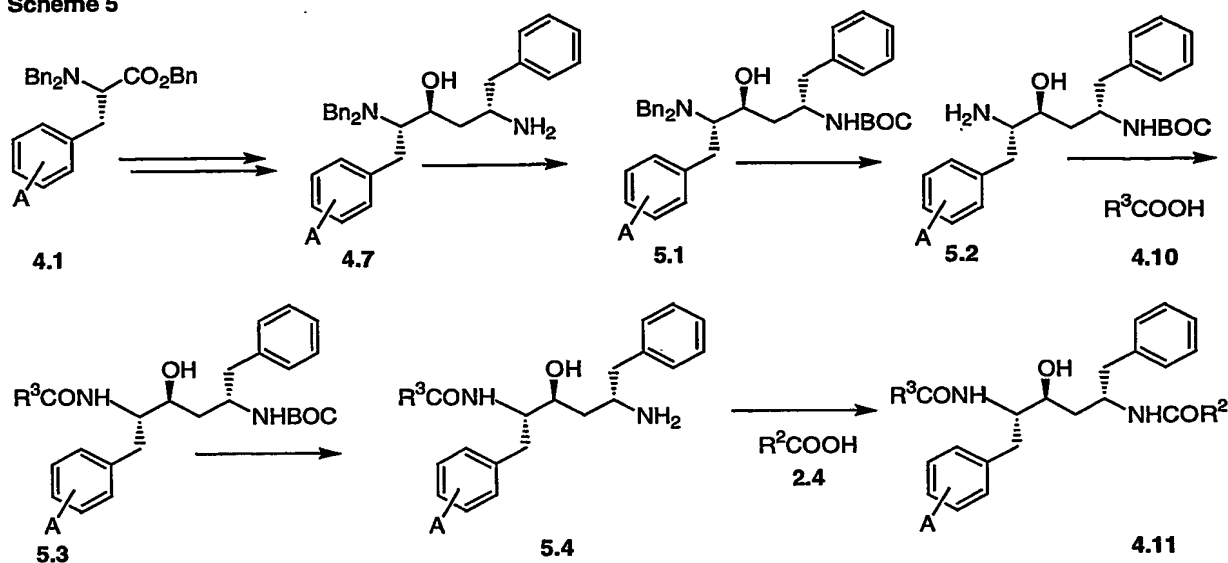
Scheme 3



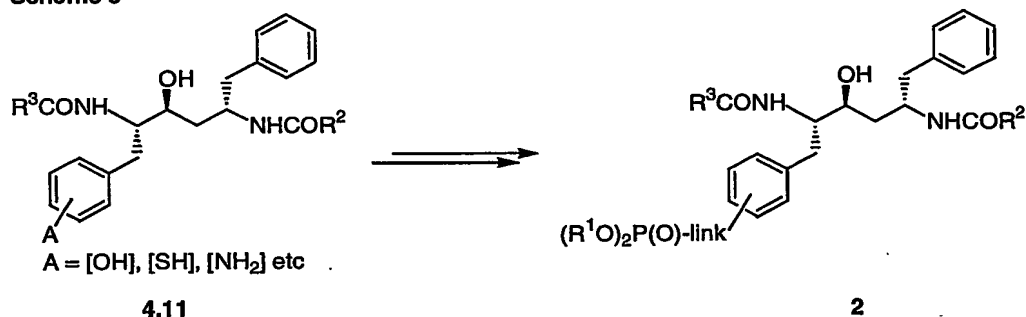
Scheme 4



Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3.

- 5 The phosphonate ester intermediate compounds 3 can be prepared by two alternative methods, illustrated in Schemes 7 and 8. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.
- As shown in Scheme 7, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile 7.1, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted
- 10 benzylmagnesium halide reagent 7.2, in which the group B is a substituent, protected if appropriate, which can be converted, after the sequence of reactions shown in Scheme 7, into the substituent link-P(O)(OR¹)₂. Examples of the substituent B are Br, [OH], [SH], [NH₂]

[CHO] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes 9-33.

The conditions for the reaction between the benzylmagnesium halide 7.2 and the ketonitrile 7.1 are similar to those described above for the preparation of the ketoenamine 4.5 (Scheme 4). Preferably, the ketonitrile 7.1 is reacted with three molar equivalents of the substituted benzylmagnesium chloride 7.2 in tetrahydrofuran at ca. 0°, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 7.3.

The thus-obtained ketoenamine 7.3 is then transformed, via the intermediate compounds 7.4, 7.5, 7.6 and 7.7 into the diacylated carbinol 7.8. The conditions for each step in the conversion of the ketoenamine 7.3 to the diacylated carbinol 7.8 are the same as those described above (Scheme 4) for the transformation of the ketoenamine 4.5 into the diacylated carbinol 4.11. The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 9-33.

Alternatively, the phosphonate esters 3 can be obtained by means of the reactions illustrated in Scheme 8. In this procedure, the amine 7.4, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative 8.1. The conditions for the introduction of the BOC group are similar to those described above for the conversion of the amine 4.7 into the BOC-protected product 5.1, (Scheme 5).

Preferably, the amine 7.4 is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 5914332, to yield the BOC-protected product 8.1.

The BOC-protected amine 8.1 is then converted, via the intermediates 8.2, 8.3 and 8.4 into the diacylated carbinol 7.8. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine 5.1 into the diacylated carbinol 4.11 (Scheme 5).

The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 18-20.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme 9 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-

5 dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **9.1**, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **9.2**. Methods for the conversion of the substituent B into the group $\text{link-P(O)(OR}^1\text{)}_2$ are described below in

10 Schemes 9 - 33.

The protected phenolic hydroxyl group present in the phosphonate-containing product **9.2** is then deprotected, using methods described below, to afford the phenol **9.3**.

The phenolic product **9.3** is then transformed into the corresponding phenoxyacetic acid **9.4**, in a two step procedure. In the first step, the phenol **9.3** is reacted with an ester of

15 bromoacetic acid **9.5**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the

20 alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **9.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described

25 in US Patent 5914332, to afford the ester **9.6**.

The thus-obtained ester **9.6** is then hydrolyzed to afford the carboxylic acid **9.4**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group,

30 methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **9.6** which R is ethyl is hydrolyzed to the carboxylic acid **9.4** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **9.7**, in which the substituent B is a precursor to the group link-P(O)(OR¹)₂, is transformed into the corresponding phenoxyacetic ester **9.8**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **9.3** into the ester **9.6**.

The phenolic ester **9.8** is then converted, by transformation of the group B into the group link-P(O)(OR¹)₂ followed by ester hydrolysis, into the carboxylic acid **9.4**. The group B which is present in the ester **9.4** may be transformed into the group link-P(O)(OR¹)₂ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes 9-14 illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids **9.8**, with, if appropriate, modifications made according to the knowledge of one skilled in the art..

Scheme 10 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **10.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **10.1** and an aminoalkyl phosphonate ester **10.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **10.2** and the aldehyde component **10.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **10.3**. The amination product **10.3** is then converted into the phenoxyacetic acid compound **10.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme 9) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **10.5** (Aldrich) and a dialkyl aminoethyl phosphonate **10.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic

acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **10.3**. The product is then converted into the acetic acid **10.8**, as described above. Using the above procedures, but employing, in place of the aldehyde **10.5**, different aldehydes **10.1**, and/or different aminoalkyl phosphonates **10.2**, the corresponding products **10.4** are
5 obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 21)

10 Scheme 11 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **11.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **11.2**. The
15 coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **11.3** is converted, using the procedures described
20 above, (Scheme 9) into the corresponding phenoxyacetic acid **11.4**. Alternatively, the olefinic product **11.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **11.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or
25 diimide. Following the reduction reaction, the product **11.5** is converted, as described above, (Scheme 9) into the corresponding phenoxyacetic acid **11.6**.

For example, 3-bromo-2,6-dimethylphenol **11.7**, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **11.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective
30 Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **11.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **11.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of

bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product **11.10**. The silyl group is removed, for example by the treatment of the ether **11.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **11.11**. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid **11.12**. Alternatively, the unsaturated compound **11.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **11.13**. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid **11.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **11.7**, different bromophenols **11.1**, and/or different dialkyl alkenyl phosphonates **11.2**, the corresponding products **11.4** and **11.6** are obtained.

Scheme 12 illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **12.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **12.2** is converted, using the procedures illustrated in Scheme 9, into the corresponding 2,6-dimethylphenoxyacetic ester **12.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **12.4**, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of **11.3**. (Scheme 11). The product **12.5** is then reduced catalytically, as described above for the reduction of **11.3**, (Scheme 11), to afford the substituted cycloalkanone **12.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate **12.7** and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate **12.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **10.3** (Scheme 10). The resultant ester **12.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **12.1**.

For example, 4-bromo-2,6-dimethylphenol **12.9** (Aldrich) is converted, as described above, into the phenoxy ester **12.10**. The latter compound is then coupled, in dimethylformamide

solution at ca. 60°, with cyclohexenone **12.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **12.12**. The enone is then reduced to the saturated ketone **12.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **12.14**, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **12.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **12.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **12.9**, different bromo-substituted 2,6-dimethylphenols **12.2**, and/or different cycloalkenones **12.4**, and/or different dialkyl aminoalkylphosphonates **12.7**, the corresponding products **12.1** are obtained.

Scheme **13** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **13.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **13.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, **13.3** is then converted, as described above (Scheme **9**) into the phenoxyacetic acid **13.4**.

For example, 2,6-dimethyl-4-mercaptophenol **13.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate **13.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **13.7**. This compound is converted, employing the procedures described above, (Scheme **9**) into the corresponding phenoxyacetic acid **13.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **13.5**, different hydroxy, thio or aminophenols **13.1**, and/or different dialkyl bromoalkyl phosphonates **13.2**, the corresponding products **13.4** are obtained.

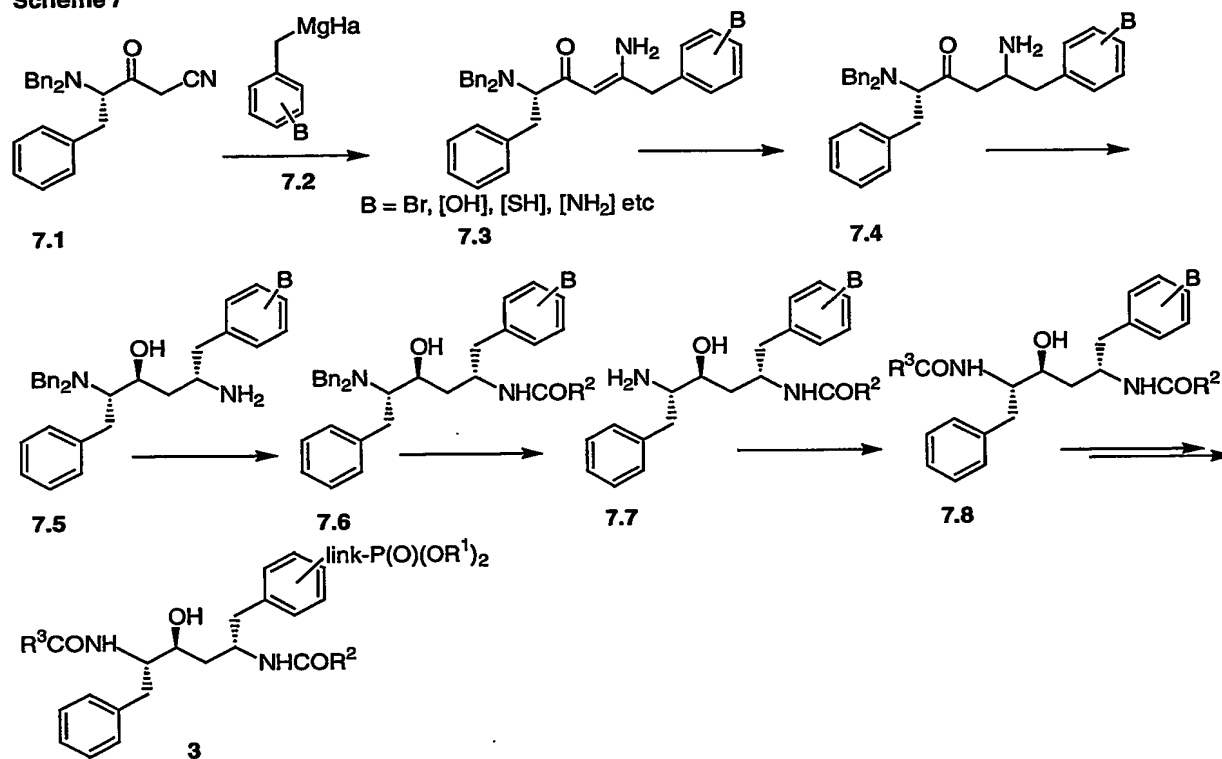
Scheme 14 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-

5 dimethylphenol 14.1 is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound 14.2. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product 14.3. The product 14.3 is then converted, using the
10 procedures described above, (Scheme 9) into the phenoxyacetic ester 14.4. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite 14.5 at ca. 100° to afford the phosphonate ester 14.6. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product 14.6 is then converted into the acetic acid 14.7 by hydrolysis of the
15 ester moiety, using the procedures described above, (Scheme 9).

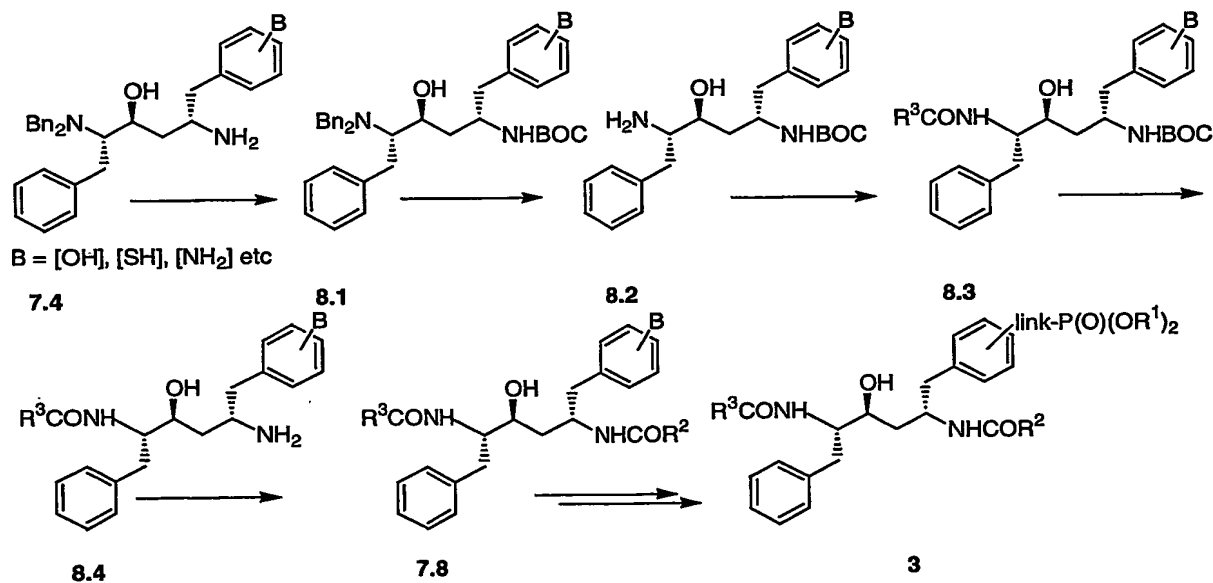
For example, 4-hydroxy-2,6-dimethylphenol 14.8 (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether 14.10. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The
20 product 14.10 is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 9) to afford the phenoxyacetic ester 14.11. This product is heated at 100° for 3 hours with three molar equivalents of triethyl phosphite 14.12, to afford the phosphonate ester 14.13. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid 14.14.

25 Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine 14.9, different bis(halomethyl) aromatic or heteroaromatic compounds 14.2, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols 14.1 and/or different trialkyl phosphites 14.5, the corresponding products 14.7 are obtained.

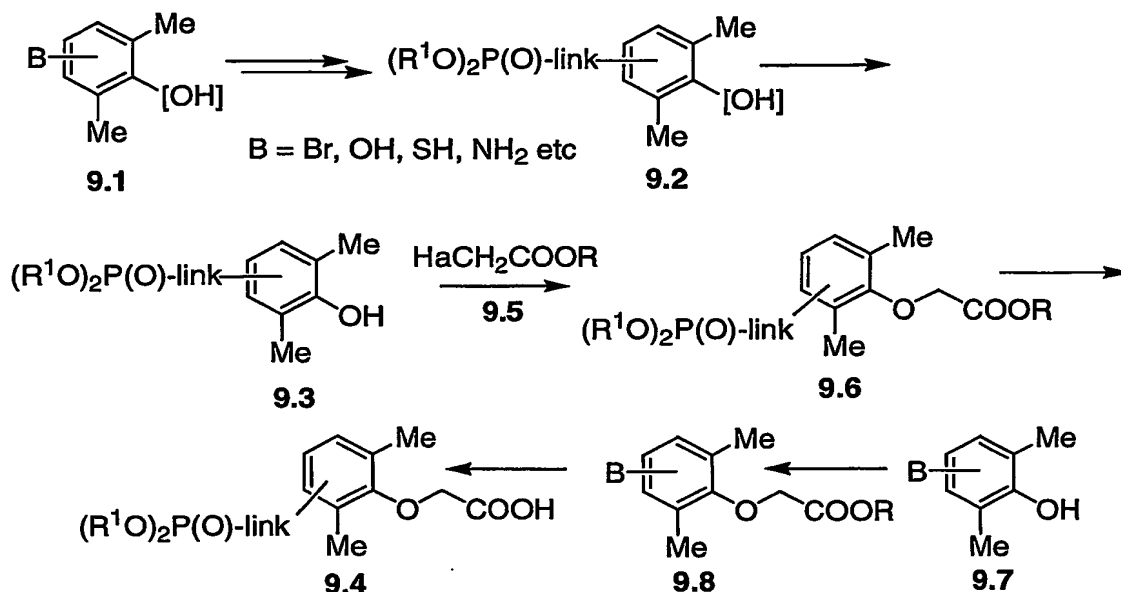
Scheme 7



Scheme 8

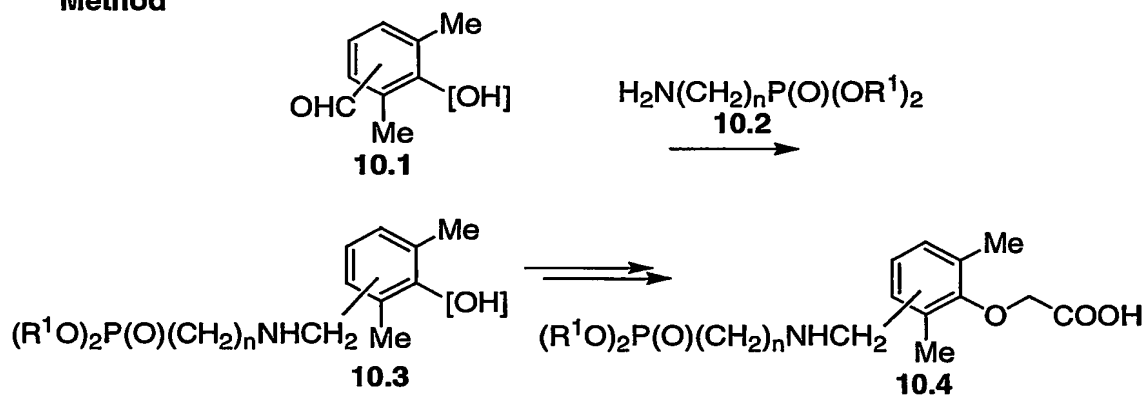


Scheme 9

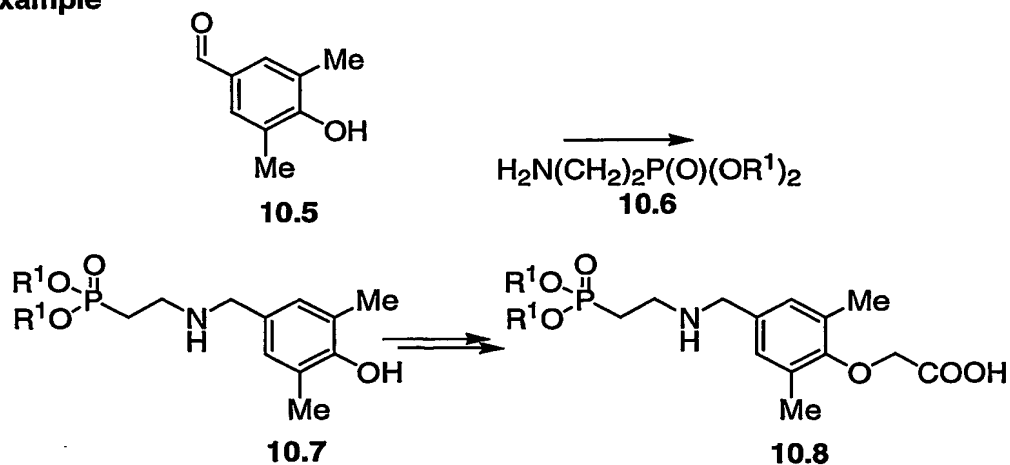


Scheme 10

Method

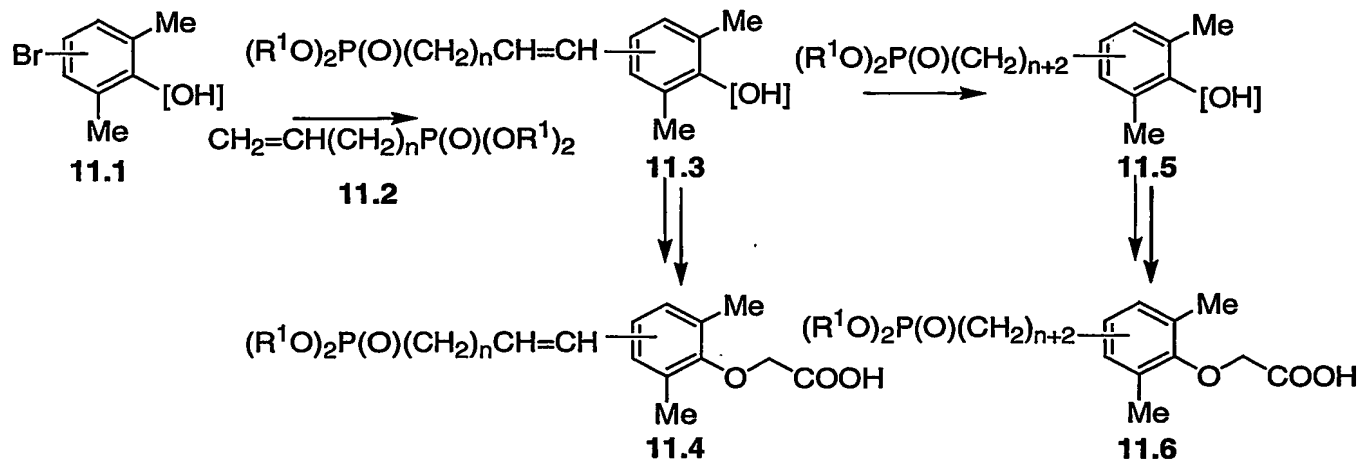


Example

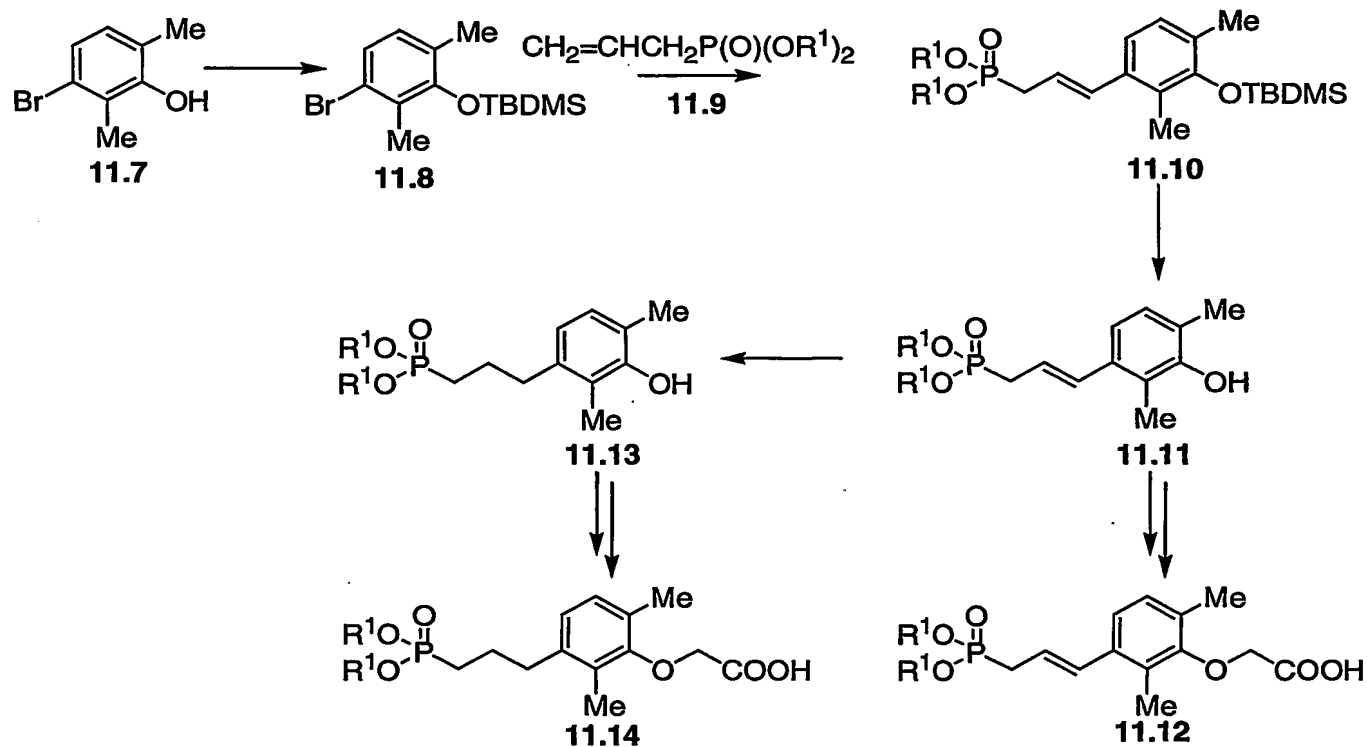


Scheme 11

Method

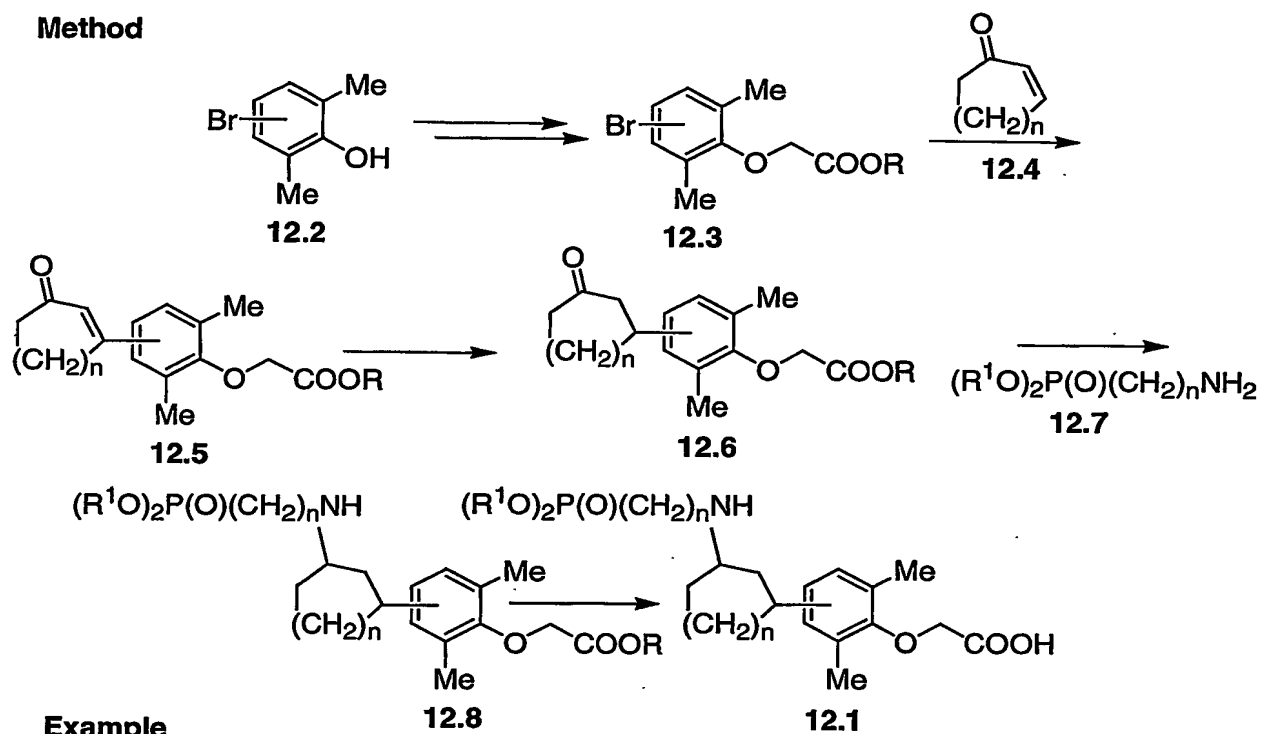


Example

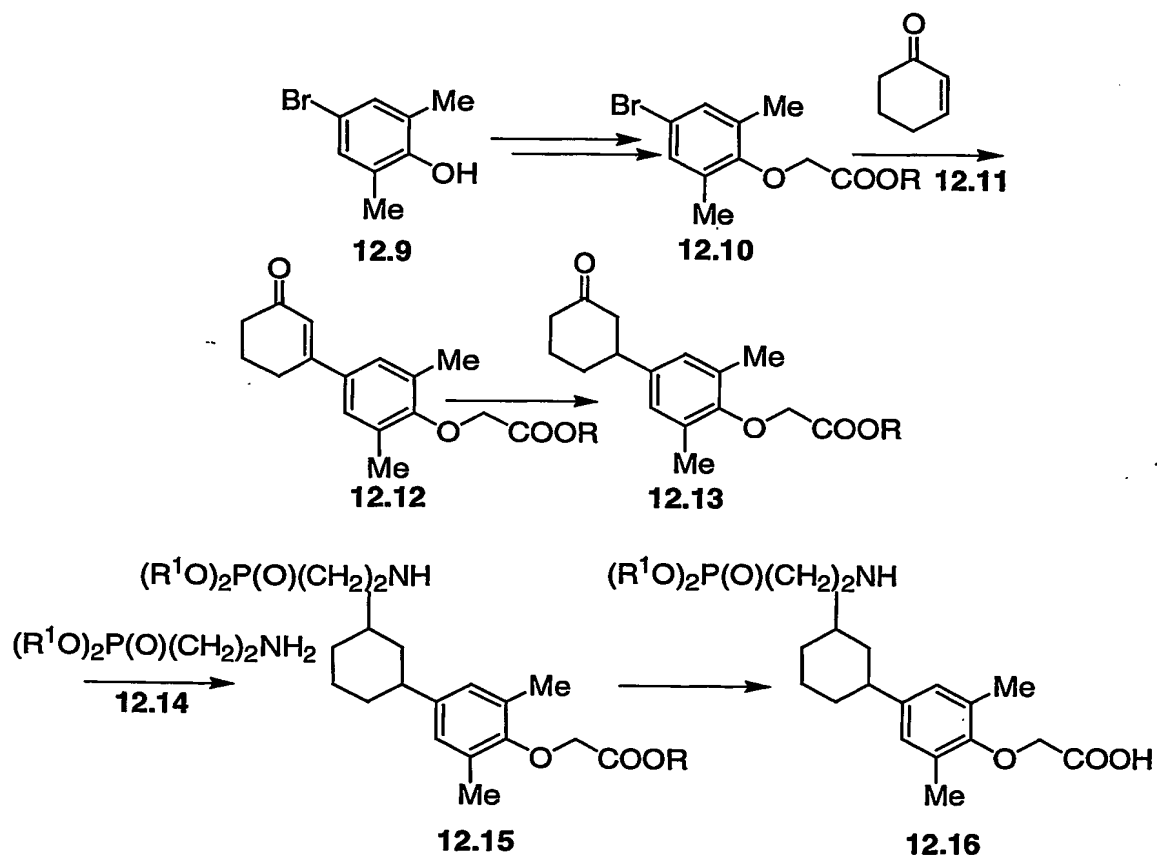


Scheme 12

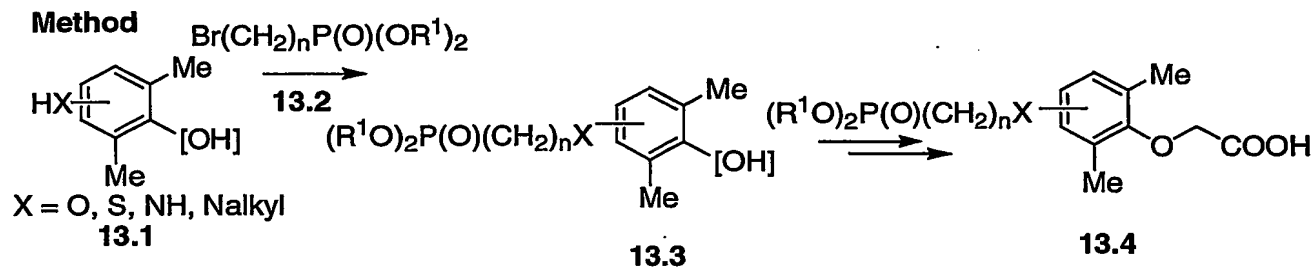
Method



Example

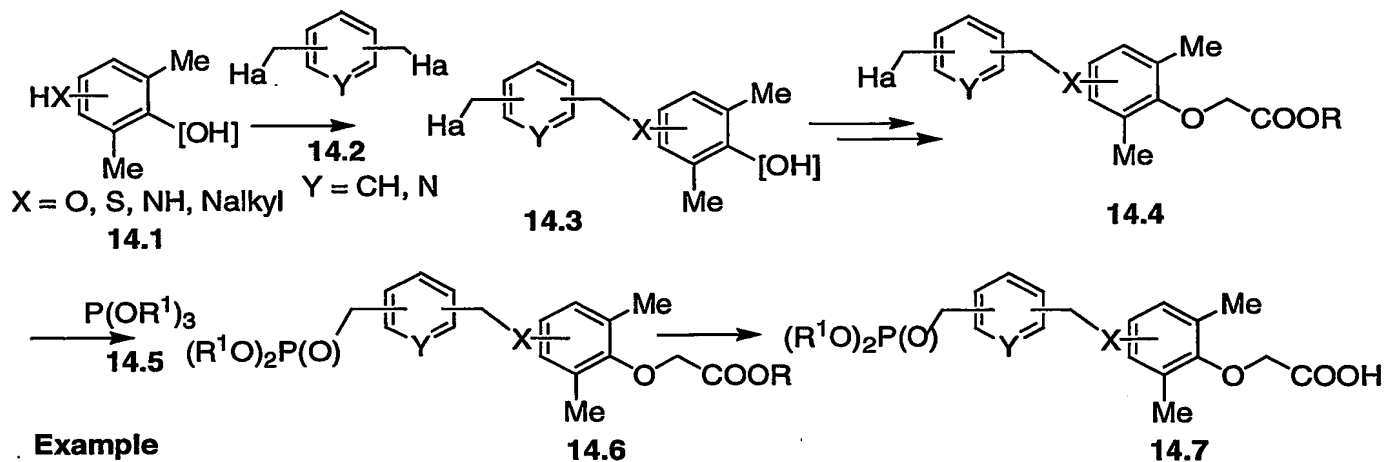


Scheme 13

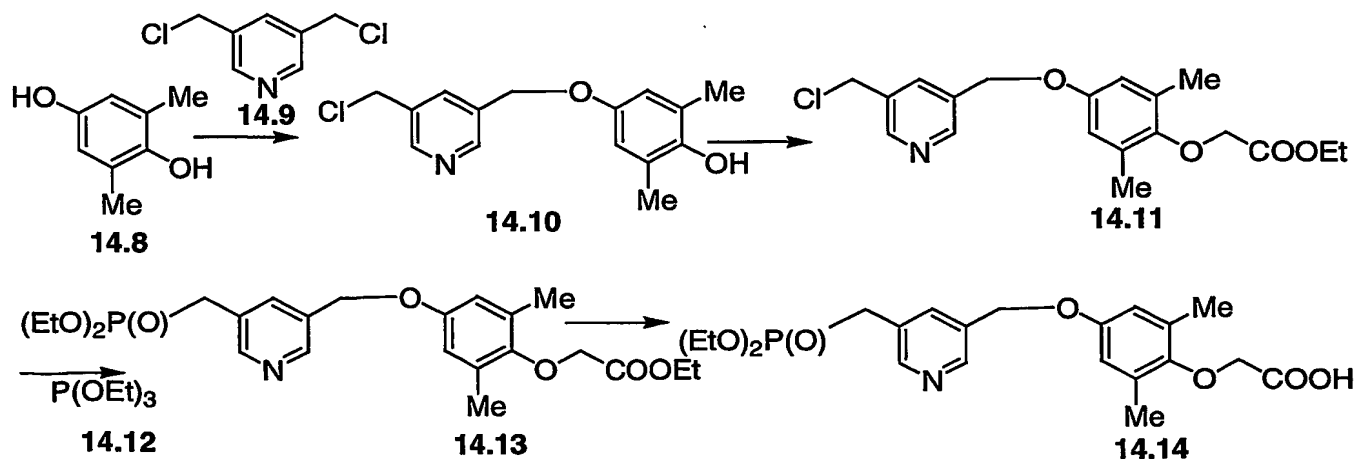


Scheme 14

Method



Example



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties, or precursors thereto.

5

Schemes 15-17 describe various methods for the preparation of phosphonate-containing analogs of phenylalanine. The compounds are then employed, as described above, (Schemes 4 and 5) in the preparation of the compounds 2.

10 Scheme 15 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 15.5.

15 In this procedure, a hydroxy or mercapto-substituted phenylalanine 15.1 is converted into the benzyl ester 15.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 15.2 is then protected. Protection methods for phenols and thiols are
20 described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable OH and SH protecting groups include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Alternative SH protecting groups include 4-methoxybenzyl and S-adamantyl. The protected hydroxy- or mercapto ester 15.3 is then reacted with a benzyl or substituted benzyl halide and
25 a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product 15.4. For example, the amine 15.3 is reacted at ca. 90° with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product 15.4, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in
30 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient

temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl protecting groups are removed by treatment with mercuric trifluoroacetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **15.5** is then reacted under various conditions to provide protected phenylalanine derivatives **15.6**, **15.7** or **15.8**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

As one option, the phenol or thiophenol **15.5** is reacted with a dialkyl bromoalkyl phosphonate **15.9** to afford the product **15.6**. The alkylation reaction between **15.5** and **15.9** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **15.6**.

For example, as illustrated in Scheme 15 Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, **15.12** is converted, as described above, into the benzyl ester **15.13**.

The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **15.14**. This compound is then converted, as described above, into the tribenzylated derivative **15.15**. The silyl protecting group is removed by treatment of **15.15** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **15.16**. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **15.17** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **15.18**.

Using the above procedures, but employing, in place of the 4-hydroxy phenylalanine **15.12**, different hydroxy or thio-substituted phenylalanine derivatives **15.1**, and/or different bromoalkyl phosphonates **15.9**, the corresponding ether or thioether products **15.6** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **15.5** is reacted with a dialkyl hydroxymethyl phosphonate **15.10** under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds **15.7**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in

Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine.

5 For example, as shown in Scheme 15, Example 2, 3-mercaptophenylalanine 15.19, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester 15.20. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether 15.21. This compound is
10 then converted, as described above for the preparation of the tribenzylated phenylalanine derivative 15.4, into the tribenzyl derivative 15.22. The 4-methoxybenzyl group is then removed by the reaction of the thioether 15.22 with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol 15.23. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a
15 dialkyl hydroxymethyl phosphonate 15.24, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product 15.25. Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative 15.19, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or different dialkylhydroxymethyl phosphonates 15.10, the corresponding products 15.7
20 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 15.5 is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate 15.11 in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base
25 such as triethylamine or cesium carbonate, to afford the ether or thioether products 15.8. For example, as illustrated in Scheme 15, Example 3, 3-hydroxyphenylalanine 15.26 (Fluka) is converted, using the procedures described above, into the tribenzylated compound 15.27. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate 15.28, prepared as
30 described in Tet. Lett., 1986, 27, 1477, to afford the ether product 15.29.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 15.26, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **15.11**, the corresponding products **15.8** are obtained.

Scheme **16** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **16.1** and a dialkyl aminoalkylphosphonate **16.2**.

In this procedure, a hydroxymethyl-substituted phenylalanine **16.3** is converted into the tribenzylated derivative **16.4** by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid **16.3** is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S.

Patent 5,491,253, to afford the product **16.4**. The latter compound is then oxidized to afford the corresponding aldehyde **16.1**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **16.1**.

For example, the carbinol **16.4** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **16.1**. This compound is reacted with a dialkyl aminoalkylphosphonate **16.2** in the presence of a suitable reducing agent to afford the amine product **16.5**. The preparation of amines by means of a reductive amination reaction is described above (Scheme 10).

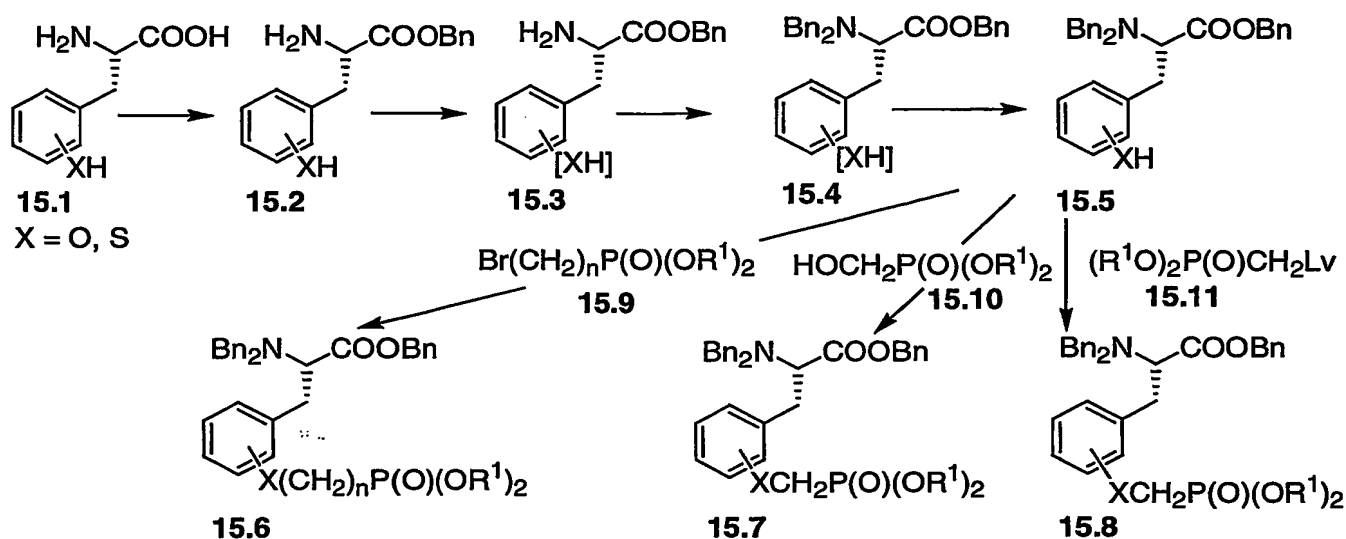
For example, 3-(hydroxymethyl)-phenylalanine **16.6**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **16.8**. This compound is then reacted, in ethanol, at ambient temperature, with one molar equivalent of a dialkyl aminoethylphosphonate **16.9**, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **16.10**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **16.6**, different hydroxymethyl phenylalanines **16.3**, and/or different aminoalkyl phosphonates **16.2**, the corresponding products **16.5** are obtained.

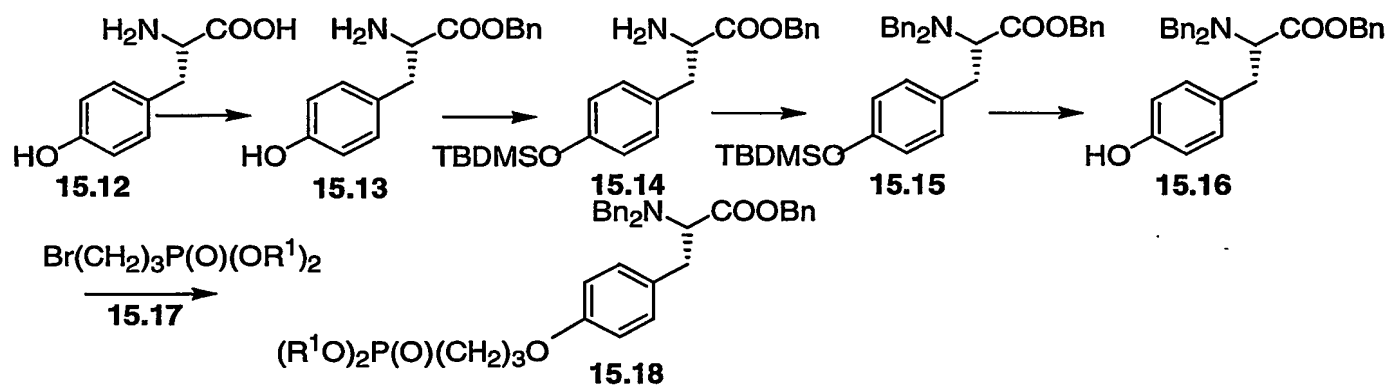
- 5 Scheme **17** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a suitably protected bromo-substituted phenylalanine **17.2** is coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **17.3** to produce the phosphonate ester **17.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl
- 10 phosphites is described in J. Med. Chem., 35, 1371, 1992.
- For example, 3-bromophenylalanine **17.5**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **15**) into the tribenzylated compound **17.6**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **17.7**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35,
- 15 1371, 1992, to afford the phosphonate product **17.8**.
- Using the above procedures, but employing, in place of 3-bromophenylalanine **17.5**, different bromophenylalanines **17.1**, and/or different dialkylphosphites **17.3**, the corresponding products **17.4** are obtained.

Scheme 15

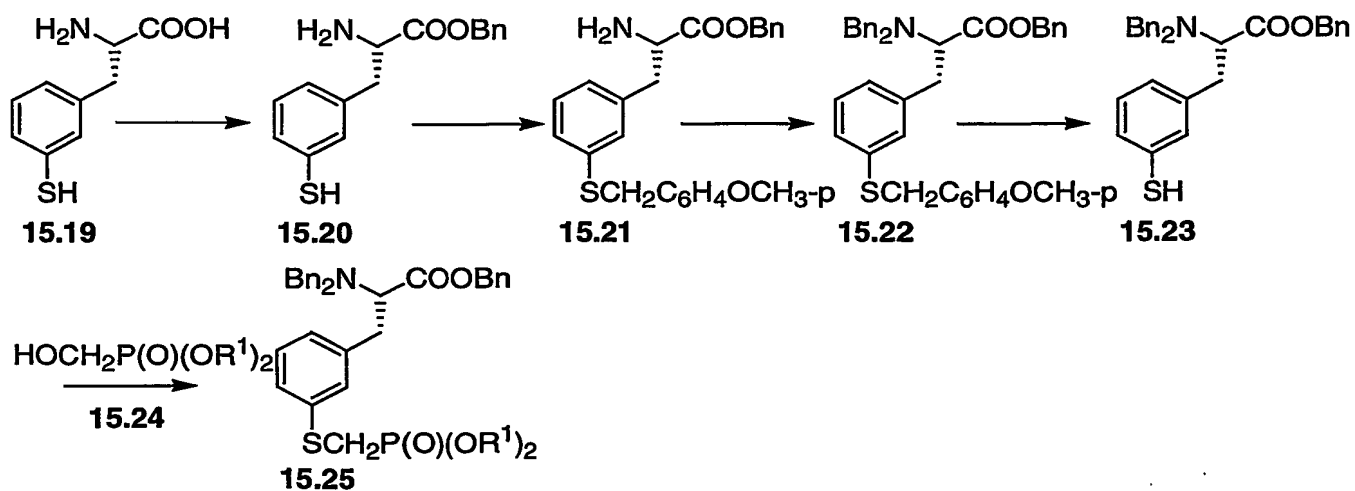
Method



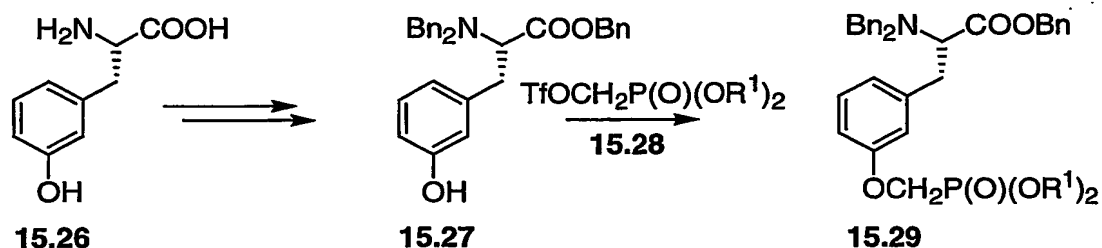
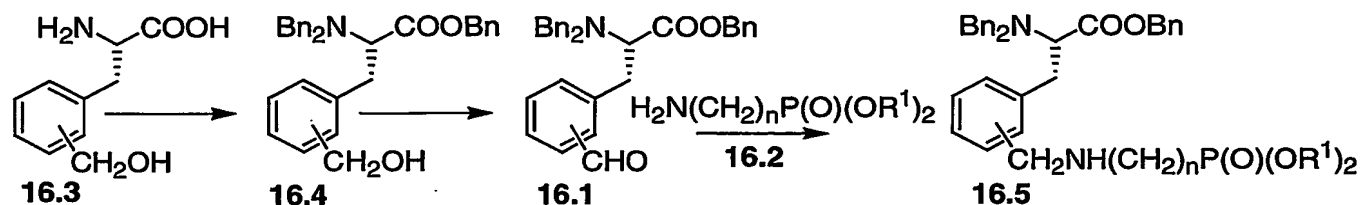
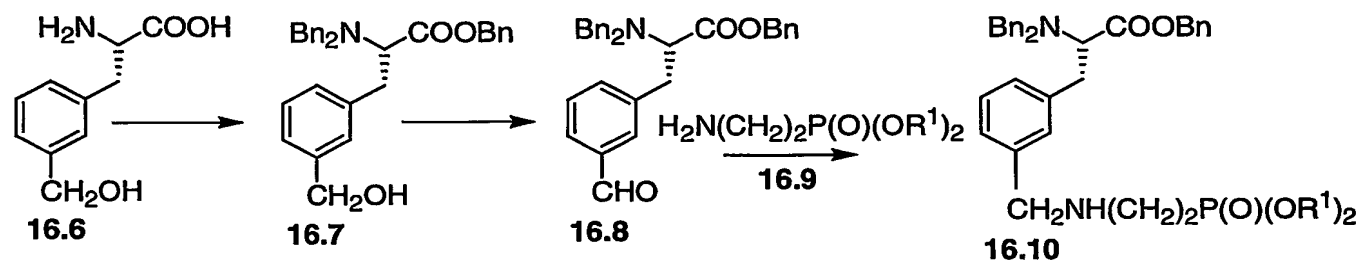
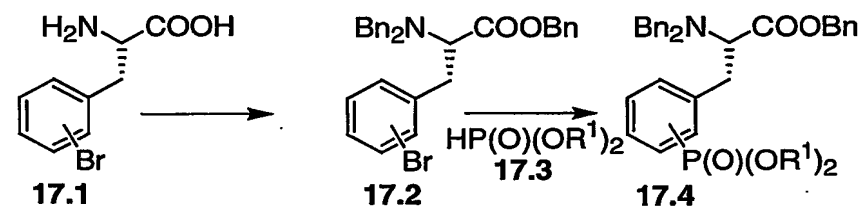
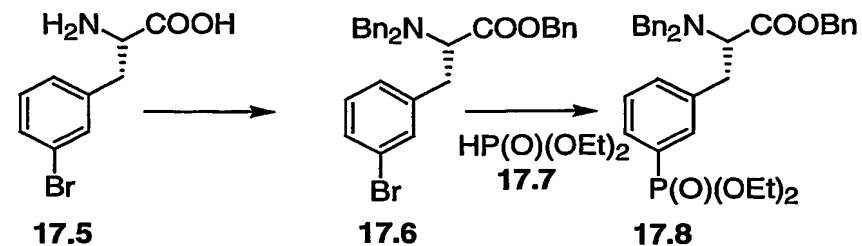
Example 1



Example 2



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Example 3**Scheme 16****Method****Example****Scheme 17****Example**

Preparation of phosphonate esters with structure 3.

Scheme 18 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile 7.1, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted, as described above (Scheme n) with a bromobenzylmagnesium halide reagent 18.1. The resultant ketoenamine 18.2 is then converted into the diacylated bromophenyl carbinol 18.3. The conditions required for the conversion of the ketoenamine 18.2 into the carbinol 18.3 are similar to those described above (Scheme 7), for the conversion of the ketoenamine 7.3 into the carbinol 7.8. The product 18.3 is then reacted with a dialkyl phosphite 17.3, in the presence of a palladium (0) catalyst, to yield the phosphonate ester 3. The conditions for the coupling reaction are the same as those described above (Scheme 17) for the preparation of the phosphonate ester 17.8.

For example, the ketonitrile 7.1 is reacted, in tetrahydrofuran solution at 0°, with three molar equivalents of 4-bromobenzylmagnesium bromide 18.4, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine 18.5. The latter compound is then converted into the diacylated bromophenyl carbinol 18.6, using the sequence of reactions described above (Scheme 7) for the conversion of the ketoenamine 7.3 into the carbinol 7.8.

The resultant bromo compound 18.6 is then reacted with diethyl phosphite 18.7 and

triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 18.8.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide 18.4, different bromobenzylmagnesium halides 18.1 and/or different dialkyl phosphites 17.3, there are obtained the corresponding phosphonate esters 3.

Scheme 19 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide 19.1, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile 7.1. The conditions for this transformation are the same as those described above (Scheme 7). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme 7) into the diacylated carbinol **19.2**. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **17.3**, to afford the phenylphosphonate **3**. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate **17.4**.

5 For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromide **19.3**. This product is then reacted with the ketonitrile **7.1**, as described above, to yield, after the sequence of reactions shown in Scheme 7, the diacylated carbinol **19.4**. The latter compound is then reacted, as described above, (Scheme 17) with a diethyl phosphite **17.3**, to afford the
10 phenylphosphonate **19.5**.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide **19.3**, different bromophenylbenzyl bromides **19.1**, and/or different dialkyl phosphites **17.3**, the corresponding products **3** are obtained.

15 Scheme 20 depicts the preparation of phosphonate esters **3** in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol **20.1** is protected, affording the derivative **20.2**. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p.
20 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as
25 described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol **20.2** is converted into a halo derivative **20.3**, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **20.2** can be transformed into the chloro compounds **20.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **20.3** is then converted into the corresponding benzylmagnesium halide **20.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **20.4** is then converted, using the sequence of reactions described above (Scheme 7) for the preparation of **7.8**, into the carbinol **20.5** in which the substituent XH is suitably protected.

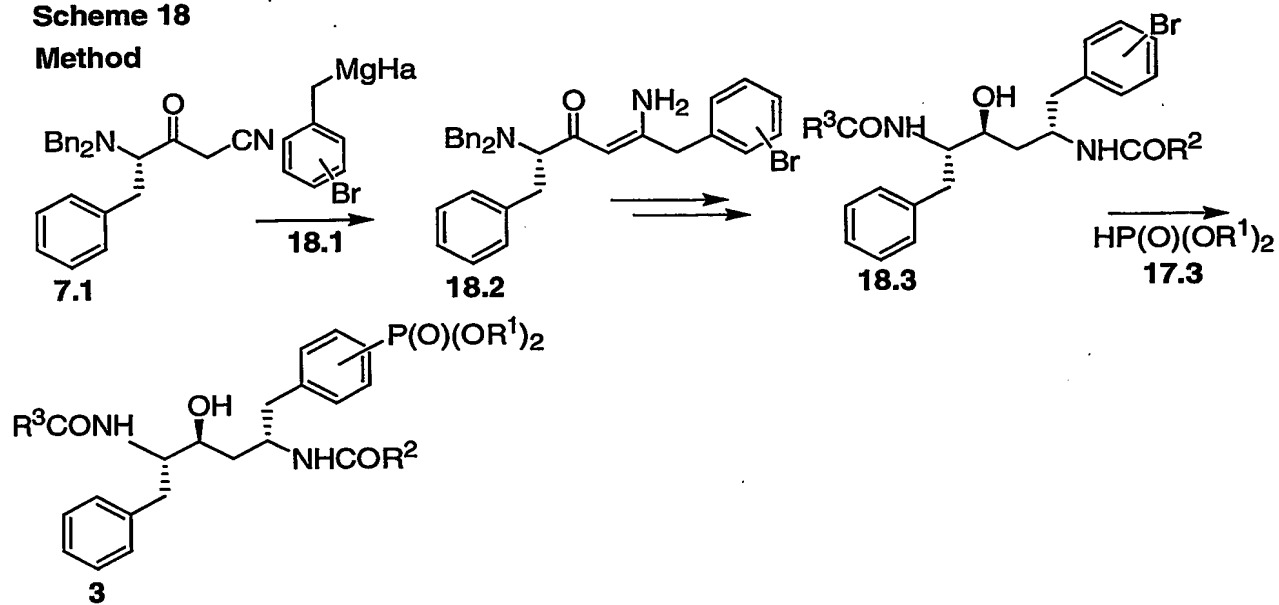
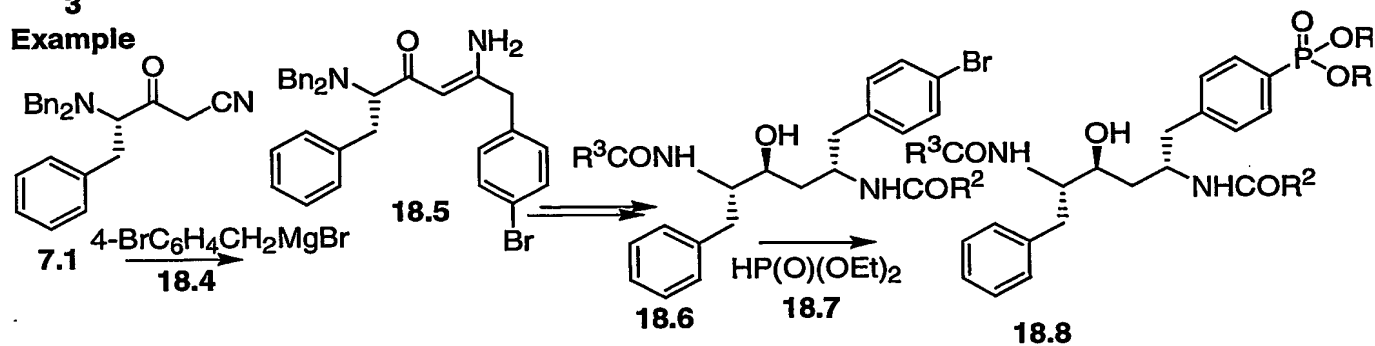
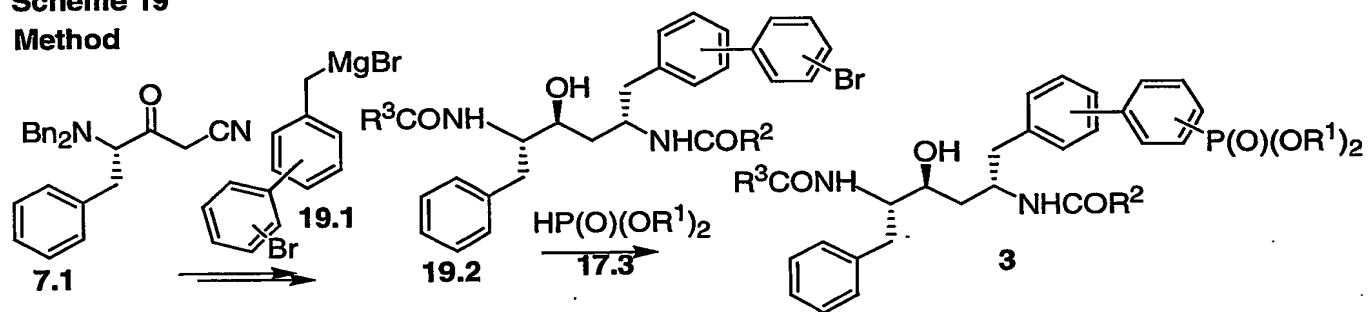
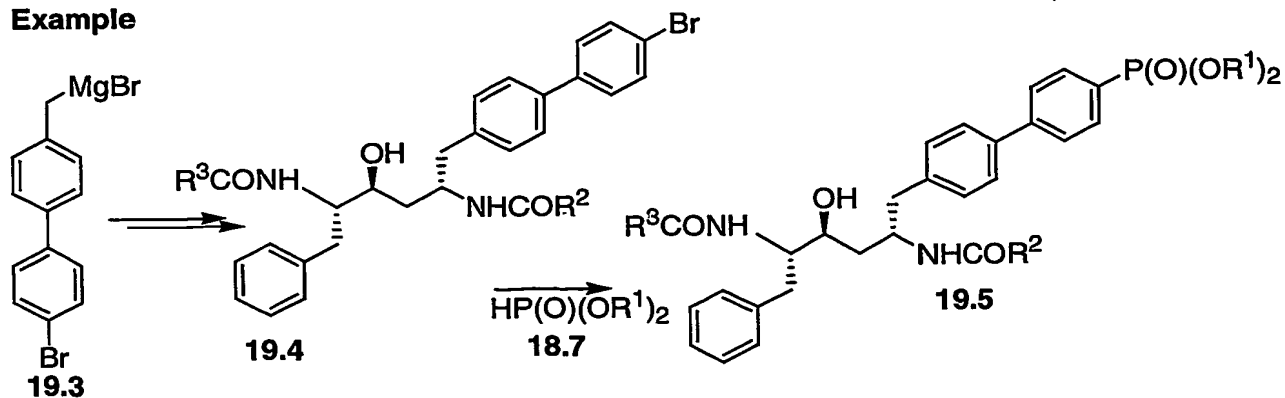
The protecting group is then removed to afford the phenol, thiophenol or amine **20.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.

For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperature, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme 1). The resultant phenol, thiophenol or amine **20.6** is then converted into the phosphonate ester **3** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **15.11**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the alkylation of the phenol **15.5** to afford the ether or thioether **15.8** (Scheme 15).

For example, 3-hydroxybenzyl alcohol **20.7** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **20.8**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the brominated product **20.9**. This material is reacted with magnesium in ether to afford the Grignard reagent **20.10**, which is then subjected to the series of reaction shown in Scheme 7 to afford the carbinol **20.11**. The triisopropylsilyl protecting group is then removed by treatment

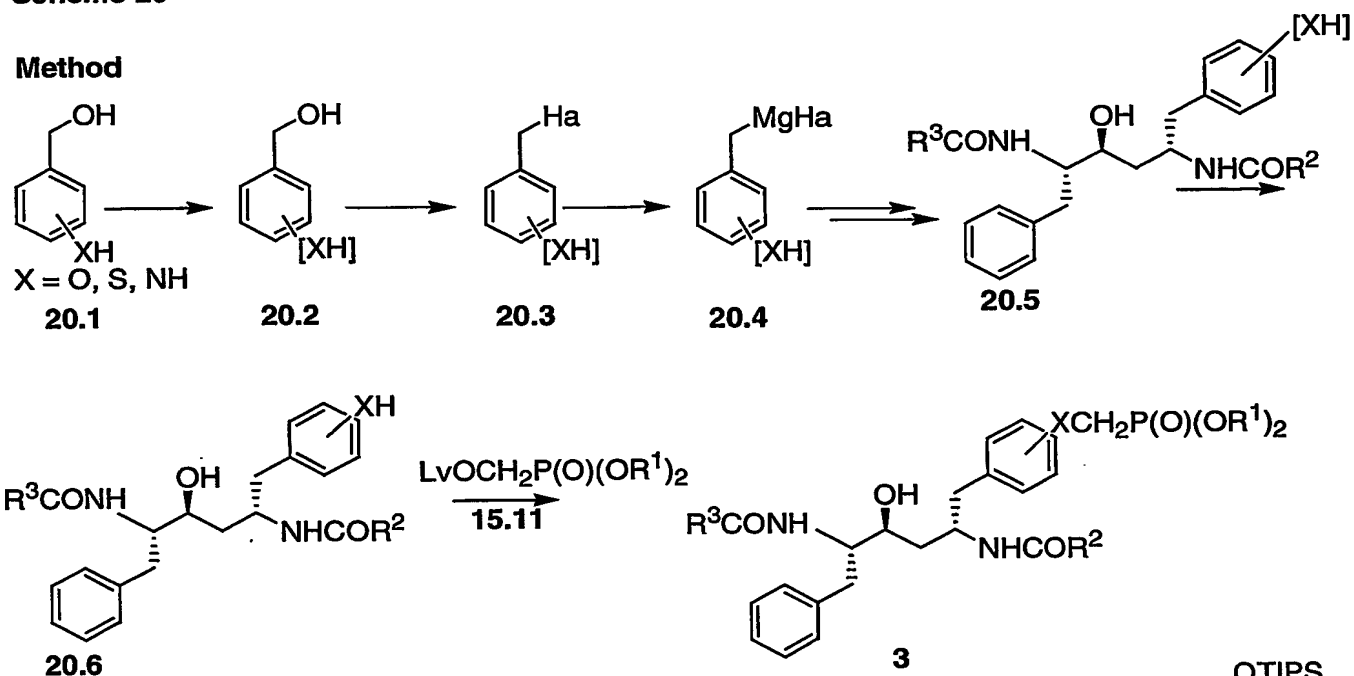
of the ether **20.11** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **20.12** is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **15.28**, prepared as described in Synthesis, 4, 327, 1998, in the presence of a base such as dimethylaminopyridine, as described above (Scheme **15**) to afford the phosphonate product **20.13**.

5 Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **20.7**, different hydroxy, mercapto or amino-substituted benzyl alcohols **20.1**, and/or different dialkyl hydroxymethyl phosphonate derivatives **15.11**, the corresponding products **3** are obtained.

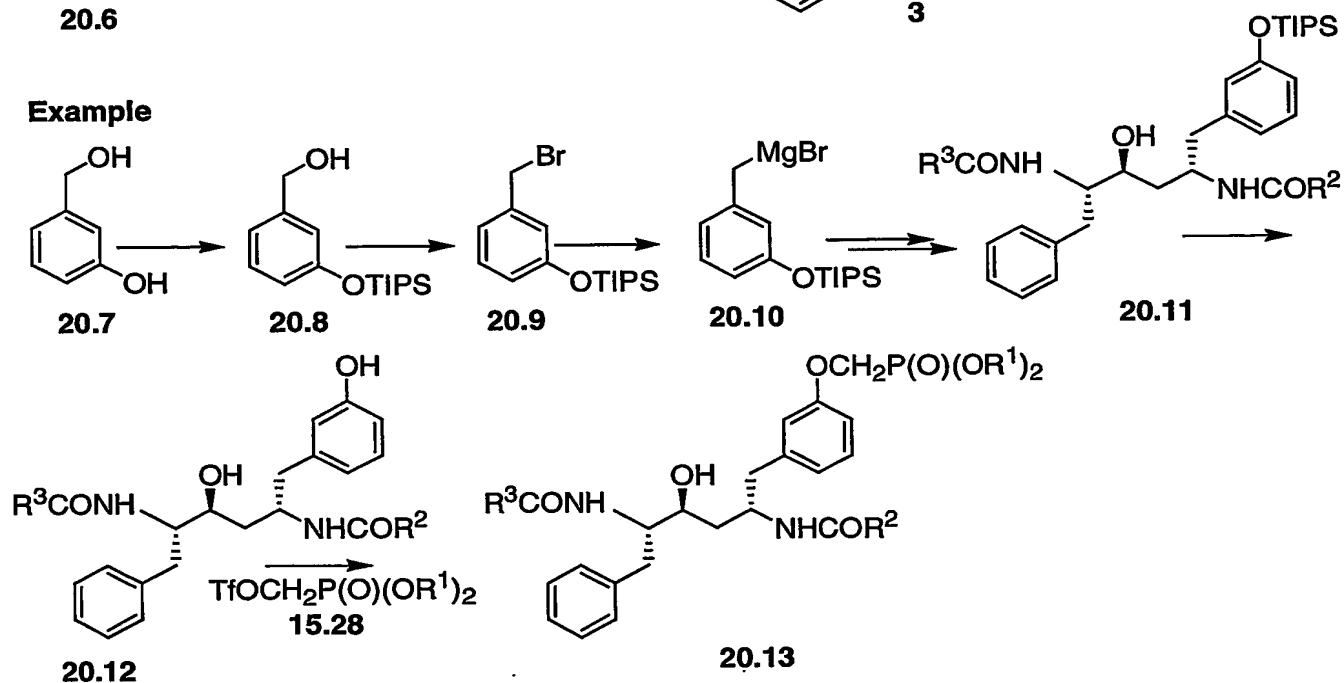
Scheme 18**Method****Example****Scheme 19****Method****Example**

Scheme 20

Method



Example



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1-33 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-5, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 21. The group R in Scheme 21 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-5 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-5. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 21.1 into the corresponding phosphonate monoester 21.2 (Scheme 21, Reaction 1) can be accomplished by a number of methods. For example, the ester 21.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 21.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 21.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 21.2 can be effected by treatment of the ester 21.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 21.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 21.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 21.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 21.1 or a phosphonate monoester 21.2 into the corresponding phosphonic acid 21.3 (Scheme 21, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **21.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **21.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **21.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **21.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **21.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **21.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

The conversion of a phosphonate monoester **21.2** into a phosphonate diester **21.1** (Scheme **21**, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **21.2** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **21.2** to the diester **21.1** can be effected by the use of the Mitsunobu reaction, as described above (Scheme 15). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **21.2** can be transformed into the phosphonate diester **21.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as

cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 21.2 is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M.

- 5 Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester 21.1.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 21, Reaction 5) by means of the methods described above of for
10 the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1, except that only one molar proportion of the component R^1OH or R^1Br is employed.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ 21.3 can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1 (Scheme 21, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and
15 triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

- Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is
20 reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 21.1.

Phosphonate esters 1-5 incorporating carbamate moieties.

- 25 The phosphonate esters 1-5 in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons C38 - C49 as shown in Chart 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p.
30 260ff.

Scheme 22 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 22, in the general reaction generating carbamates, a carbinol 22.1 is converted into the activated derivative 22.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 22.2 is then reacted with an amine 22.3, to afford the carbamate product 22.4. Examples 1 – 7 in Scheme 22 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 22, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 22.5. In this procedure, the carbinol 22.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 22.6. The latter compound is then reacted with the amine component 22.3, in the presence of an organic or inorganic base, to afford the carbamate 22.7. For example, the chloroformyl compound 22.6 is reacted with the amine 22.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 22.7. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 22, Example 2 depicts the reaction of the chloroformate compound 22.6 with imidazole, 22.7, to produce the imidazolide 22.8. The imidazolide product is then reacted with the amine 22.3 to yield the carbamate 22.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 22 Example 3, depicts the reaction of the chloroformate 22.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 22.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 22.19 - 22.24 shown in Scheme 22, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 22.19, N-hydroxysuccinimide 22.20, or pentachlorophenol, 22.21, the mixed carbonate 22.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 22.22 or 2-hydroxypyridine 22.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

5 Scheme 22 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 22.8 is employed. In this procedure, a carbinol 22.5 is reacted with an equimolar amount of carbonyl diimidazole 22.11 to prepare the intermediate 22.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 22.8 is then reacted with an equimolar amount of the
10 amine R'NH₂ to afford the carbamate 22.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 22.7.

Scheme 22, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 22.13. In this procedure, a carbinol ROH is reacted at ambient
15 temperature with an equimolar amount of benzotriazole carbonyl chloride 22.12, to afford the alkoxy carbonyl product 22.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
20 to about 80° as described in Syn., 1977, 704.

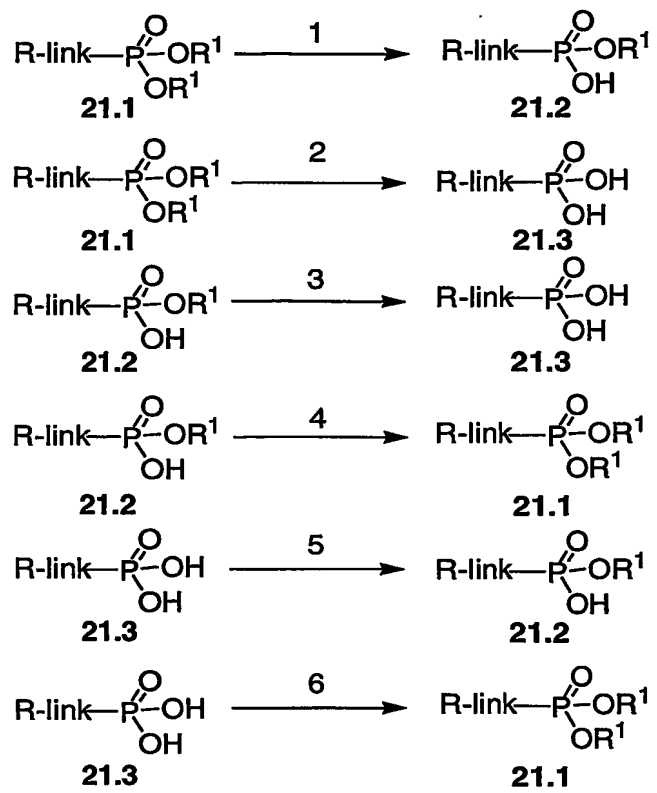
Scheme 22, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 22.14, is reacted with a carbinol 22.5 to afford the intermediate alkyloxycarbonyl intermediate 22.15. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The procedure in which the reagent 22.15 is derived from
25 hydroxybenzotriazole 22.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 22.15 is derived from N-hydroxysuccinimide 22.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 22.15 is derived from 2-hydroxypyridine 22.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 22.15 is derived from 4-nitrophenol 22.24 is described in Syn. 1993, 103. The reaction between equimolar amounts
30 of the carbinol ROH and the carbonate 22.14 is conducted in an inert organic solvent at ambient temperature.

Scheme 22, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 22.16. in this procedure, an alkyl chloroformate 22.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 22.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 22.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 22, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 22.7.

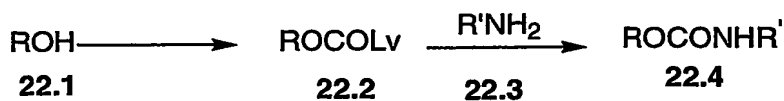
Scheme 22, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 22.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 22.7.

Scheme 22, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 22.7.

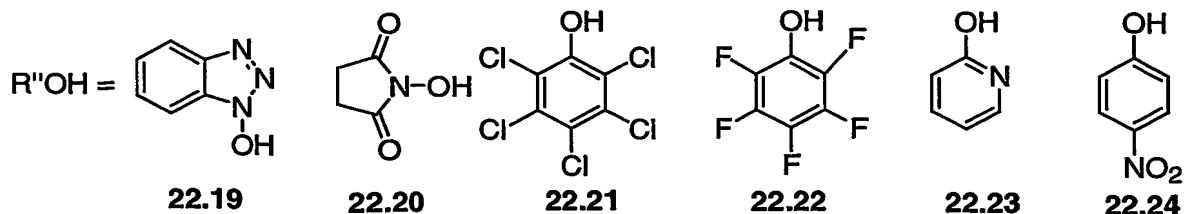
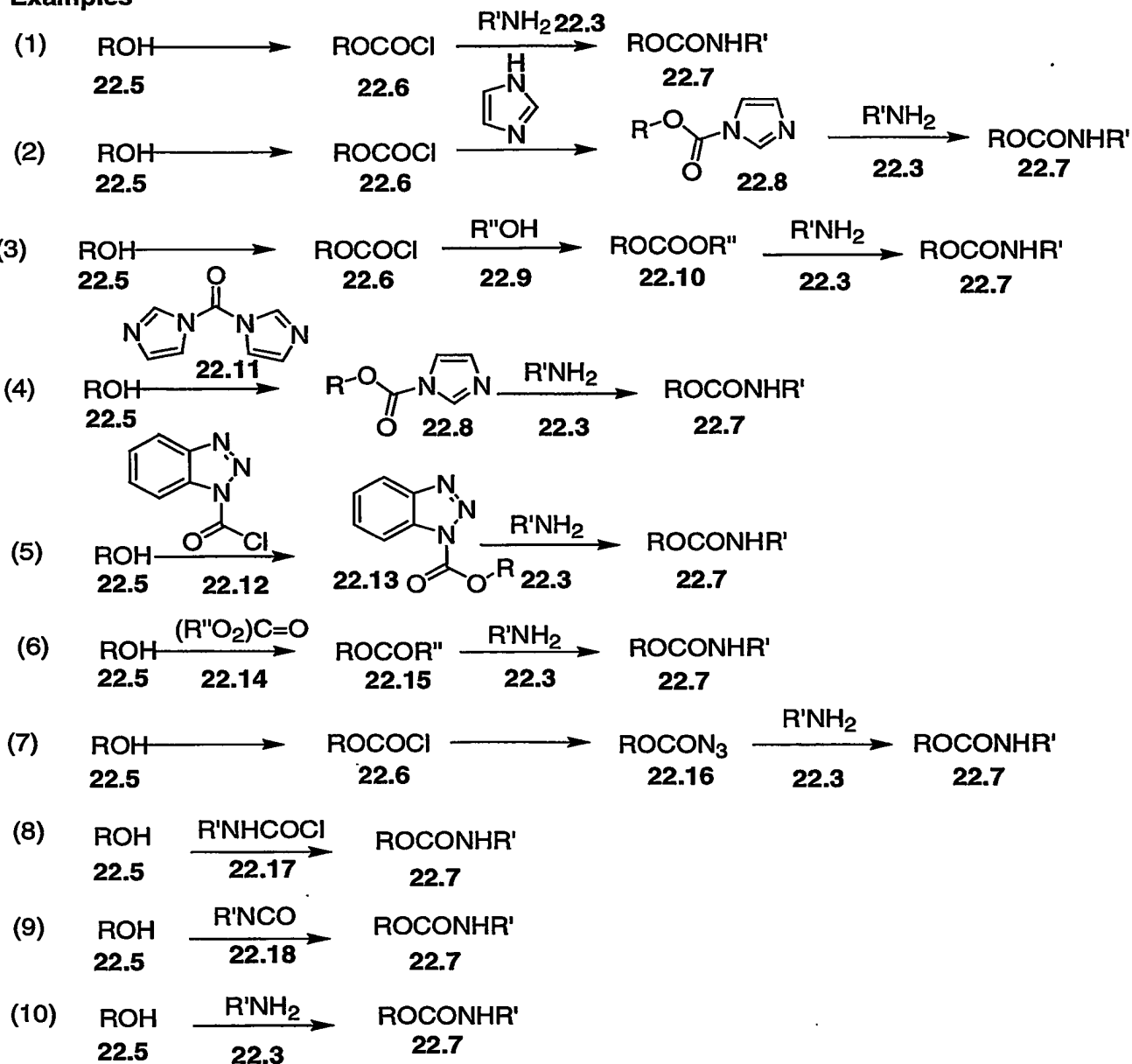
Scheme 21

Scheme 22

General reaction



Examples



Preparation of phosphonate intermediates 4 and 5 with phosphonate moieties incorporated into the groups R^2COOH and R^3COOH .

5 The chemical transformations described in Schemes 1-22 illustrate the preparation of compounds 1-3 in which the phosphonate ester moiety is attached to the dimethylphenoxyacetyl (R^3) substructure, (Schemes 1-3), the phenylalanine moiety (Schemes 4-6), and the benzyl moiety (Schemes 7, 8).

The various chemical methods employed herein (Schemes 9-22) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH , as defined in Charts 2a, 2b, and 2c. The resultant phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 4 and 5. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes 4, 5 and 22) for the introduction of the R^2CO and R^3CO moieties.

For example, Schemes 23 - 27 illustrate methods for the preparation of hydroxymethyl-substituted benzoic acids (structure C25, Chart 2b) incorporating phosphonate moieties; Schemes 28-30 illustrate the preparation of tetrahydropyrimidine aminoacid derivatives (structure C27, Scheme 2b) incorporating phosphonate ester moieties, and Schemes 31-33 show the syntheses of benzyl carbamate aminoacid derivatives (structure C4, Chart 2a) incorporating phosphonate ester moieties. The thus-obtained phosphonate ester synthons are then incorporated into the compounds 4 and 5.

Scheme 23 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 23.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 23.2. This compound is reacted with a chlorodialkyl phosphite 23.3 to yield the phenylphosphonate ester 23.4, which upon deprotection affords the carboxylic acid 23.5.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, 23.6, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The

acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **23.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **23.8**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **23.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **23.10**. Halogen-metal exchange is performed by the reaction of **23.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **23.3**, to produce the phosphonate **23.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **23.12**.

Using the above procedures, but employing, in place of the bromo compound **23.6**, different bromo compounds **23.1**, there are obtained the corresponding products **23.5**.

Scheme **24** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, **24.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **24.2** is reacted with a sodium dialkyl phosphite, **24.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **24.4**. Deprotection of the carboxyl function then yields the carboxylic acid **24.5**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **24.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p17, to afford the ether ester **24.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **24.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **24.8**. This compound is then reacted with a sodium dialkyl phosphite **24.3** in tetrahydrofuran, as described above, to afford the phosphonate **24.9**.

Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **24.10**.

Using the above procedures, but employing, in place of the methyl compound **24.6**, different methyl compounds **24.1**, there are obtained the corresponding products **24.5**.

Scheme **25** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid **25.1** is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **25.2**, to afford the coupled product **25.3**, which upon deprotection affords the carboxylic acid **25.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **25.6**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **25.7**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77, to afford the mono-silyl ether **25.8**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **25.2**, under the conditions of the Mitsunobu reaction, as described above (Scheme **15**) to afford the coupled product **25.9**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **25.10**.

Using the above procedures, but employing, in place of the phenol **25.6**, different phenols or thiophenols **25.1**, there are obtained the corresponding products **25.4**.

Scheme **26** depicts the preparation of phosphonate esters attached to the

hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate **26.2** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **26.1**. The product **26.3** can be deprotected to afford the phosphonate **26.4**, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid **26.5**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **26.6**, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **26.7**. This

compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **26.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above (Scheme 11) to afford the product **26.9**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **26.10** and **26.11**.

Using the above procedures, but employing, in place of the bromo compound **26.6**, different bromo compounds **26.1**, and/or different phosphonates **26.2**, there are obtained the corresponding products **26.4** and **26.5**.

Scheme 27 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **27.1** is converted to the corresponding boronic acid **27.2**, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **27.3**. The product **27.4** is then deprotected to afford the diaryl phosphonate product **27.5**.

For example, the silylated OBO ester **27.6**, prepared as described above, (Scheme 23), is converted into the boronic acid **27.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **27.8**, prepared as described in J. Chem. Soc. Perkin

Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **27.9**. Deprotection, as described above, then affords the benzoic acid **27.10**.

Using the above procedures, but employing, in place of the bromo compound **27.6**, different bromo compounds **27.1**, and/or different phosphonates **27.3**, there are obtained the corresponding carboxylic acid products **27.5**.

Scheme 28 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid **C27** in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom O, S, or N. In this procedure, an amino acid **28.1**, in which R⁴ is as defined in Chart 2b, is converted into the corresponding phenyl carbamate **28.2**. The preparation of phenyl carbamates is described in Tet. Lett., 1977, 1936, and in J. Chem. Soc., C, 1967, 2015. The amine substrate is reacted with phenyl chloroformate in the presence of an inorganic or

organic base, such as potassium carbonate or triethylamine, in an organic, aqueous or aqueous organic solvent such as dichloromethane, tetrahydrofuran or water or pyridine. Preferably, the aminoacid **28.1** is reacted with phenyl chloroformate, in water containing lithium hydroxide, lithium chloride and alumina, at a pH of about 9.5, as described in Org. Process Res. Dev., 2000, 4, 264, to afford the phenyl carbamate **28.2**. This compound is then reacted with di(3-chloropropyl)amine **28.3**, prepared as described in Tet. 1995, 51, 1197, to afford the amide product **28.4**. The preparation of amides by reaction of an ester with an amide is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The displacement reaction is effected by treatment of the substrate with the amine, optionally in the presence of a base such as sodium methoxide and the like, to afford the amide product **28.4**. Preferably, the carbamate **28.2** and the amine **28.3** are reacted together in tetrahydrofuran, in the presence of sodium hydroxide or lithium hydroxide, to produce the amide product **28.4**. The latter compound is then transformed, optionally without isolation, into the chloropropyl-substituted tetrahydropyrimidine product **28.5**, by reaction with a strong base such as potassium tert. butoxide in tetrahydrofuran, as described in Org. Process. Res. Dev., 2000, 4, 264. The compound **28.5** is then reacted with a dialkyl hydroxy, mercapto or alkylamino-substituted alkylphosphonate **28.6** to afford the displacement product **28.7**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as sodium hydride, lithium hexamethyldisilazide, potassium carbonate or the like, optionally in the presence of a catalytic amount of potassium iodide, to afford the ether, thioether or amine product **28.7**.

Alternatively, the chloropropyl-substituted tetrahydropyrimidine compound **28.5** is transformed into the corresponding propylamine **28.8**. The conversion of halo derivatives into amines is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397ff, or Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 665ff. The chloro compound is reacted with ammonium hydroxide, anhydrous ammonia or hexamethylene tetramine, or with an alkali metal amide such as sodamide to afford the amine product. Preferably, the chloro compound is reacted with potassium phthalimide, and the phthalimido product is then cleaved by treatment with hydrazine, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 679, to afford the amine **28.8**. The product is then subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **28.9**, to yield the phosphonate product **28.10**.

For example, as shown in Scheme 28, Example 1, 3-methyl-2-phenoxy-carbonylamino-butyr-
ic acid **28.11**, prepared as described in Org. Process Res. Dev., 2000, 4, 264, is reacted with
di(3-chloropropyl)amine, using the conditions described above, to afford 2-[3,3-bis-(3-chloro-
propyl)-ureido]-3-methyl-butyr-ic acid **28.4**. The product is then reacted sequentially with
5 sodium hydroxide and then potassium tert. butoxide in tetrahydrofuran, as described in Org.
Process Res. Dev., 2000, 4, 264, so as to afford the cyclized product 2-[3-(3-chloro-propyl)-
2-oxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyr-ic acid **28.13**. The latter compound is then
reacted in dimethylformamide solution at about 70°, with a dialkyl 2-mercaptoethyl
phosphonate **28.14**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, potassium
10 carbonate and a catalytic amount of potassium iodide, to yield the phosphonate ester **28.13**.
Using the above procedures, but employing, in place of the valine carbamate **28.11**, different
carbamates **28.2**, and/or different hetero-substituted alkyl phosphonates **28.6**, the
corresponding products **28.7** are obtained.

As a further illustration, Scheme 28, Example 2 depicts the reaction of the chloropropyl
15 tetrahydropyrimidine derivative **28.13** with potassium phthalimide **28.16**. Equimolar amounts
of the reactants are combined in dimethylformamide at ca 80°, in the presence of a catalytic
amount of potassium iodide, to afford 2-{3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-
2-oxo-tetrahydro-pyrimidin-1-yl}-3-methyl-butyr-ic acid **28.17**. The product is then reacted
under reductive amination conditions, as described above (Scheme 10) with a dialkyl
20 formylphenyl phosphonate **28.19** (Epsilon) to yield the phosphonate ester product **28.20**.
Using the above procedures, but employing, in place of the valine carbamate **28.11**, different
carbamates **28.2**, and/or different formyl-substituted alkyl phosphonates **28.9**, the
corresponding products **28.10** are obtained.

25 Scheme 29 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid
C27 in which the phosphonate moiety is attached by means of an alkylene chain. In this
procedure, an amino acid **29.1** is subjected to an alkylation reaction with a propanol derivative
29.2 in which Lv is a leaving group such as halo or sulfonyl. The reaction is conducted in
aqueous or aqueous organic solution in the presence of a base such as sodium hydroxide,
30 potassium carbonate and the like, to afford the product **29.3**. This compound is then oxidized
to the corresponding aldehyde **29.4**. The conversion of alcohols to aldehydes is described, for
example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff.

Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as pyridine, dichloromethane or toluene. Preferably, the alcohol **29.3** is reacted with an equimolar amount of pyridinium chlorochromate in dichloromethane at ambient temperature, to afford the aldehyde **29.4**. This material is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate **29.5**, using the conditions described above (Scheme 10) to produce the phosphonate ester **29.6**. The latter compound is then reacted with phosgene, or carbonyldiimidazole or an equivalent reagent, to yield the tetrahydropyrimidine product **29.7**. Equimolar amounts of the reagents are combined in an inert polar solvent such as tetrahydrofuran or dimethylformamide at ambient temperature, to effect the cyclization reaction.

For example, 2-(3-hydroxy-propylamino)-3-methyl-butyric acid, the preparation of which is described in Toxicol. Appl. Pharm., 1995, 131, 73, is oxidized, as described above, to afford 3-methyl-2-(3-oxo-propylamino)-butyric acid **29.9**. The product is then reacted with a dialkyl aminoethyl phosphonate **29.10**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, under reductive amination conditions, to give the product **29.11**. This compound is then reacted one molar equivalent of carbonyldiimidazole in dichloromethane, as described in US Patent 5914332, to afford the tetrahydropyrimidine product **29.12**.

Using the above procedures, but employing, in place of the valine derivative **29.8**, different aminoacid derivatives **29.3**, and/or different amino-substituted alkyl phosphonates **29.5**, the corresponding products **29.7** are obtained.

Scheme 30 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid **C27** in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a tetrahydropyrimidine aminoacid derivative, prepared as described in U.S. Patent 5,914,332, is converted into the carboxyl-protected compound **30.2**. The protection and deprotection of carboxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. For example, the carboxyl group is protected as a benzyl or substituted benzyl ester, removable by means of hydrogenolysis, or as a tert. butyl ester, removable by treatment with anhydrous acid. The carboxyl-protected derivative **30.2** is then reacted with a dialkyl bromoalkyl phosphonate **30.3**, in the presence of a strong base such as sodium hydride, potassium tert. butoxide, lithium

hexamethyldisilazide and the like, in a polar solvent such as dimethylformamide, to afford the alkylation product **30.4**. The carboxyl group is then deprotected to yield the carboxylic acid **30.5**.

For example, 3-methyl-2-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-butyric acid **30.6**,

prepared as described in Org. Process Res. Dev., 200, 4, 264, is converted into the benzyl ester **30.7** by reaction with benzyl alcohol, dicyclohexylcarbodiimide and

dimethylaminopyridine in dichloromethane, as described in J. Chem. Soc. Chem. Comm., 1982, 1132. The product is then treated with one molar equivalent of lithium

hexamethyldisilazide in dimethylformamide, and the resultant anion is reacted with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **30.8** (Aldrich), to prepare the alkylated product **30.9**. The benzyl ester is then converted into the carboxylic acid **30.10**, by hydrogenolysis over a palladium catalyst, as described in Org. React., VII, 263, 1953.

Using the above procedures, but employing, in place of the valine derivative **30.6**, different aminoacid derivatives **30.1**, and/or different bromo-substituted alkyl phosphonates **30.3**, the corresponding products **30.5** are obtained.

Scheme 31 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid **C4** (Chart 2a) in which the phosphonate group is attached by means of an alkylene chain and a heteroatom O, S or N. In this procedure, a substituted benzyl alcohol **31.1** is reacted with a dialkyl bromoalkyl phosphonate **31.2** to prepare the ether, thioether or amine product **31.3**. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium carbonate, optionally in the presence of a catalytic amount of potassium iodide. The benzyl alcohol product **31.3** is then transformed into a formyl derivative **31.4**, in which Lv is a leaving group, as described above (Scheme 22). The formate derivative **31.4** is then reacted with a carboxy-protected amino acid **31.5**, using the procedures described above for the preparation of carbamates (Scheme 22), to afford the carbamate product **31.6**. The carboxy-protecting group is then removed to afford the carboxylic acid **31.7**. The carboxyl protecting group present in the aminoacid **31.5** is selected so that the conditions for removal do not cleave the benzyl carbamate moiety in the substrate **31.6**.

For example, 3-methylaminobenzyl alcohol **31.8** is reacted in dimethylformamide solution at ca 70° with one molar equivalent of a dialkyl bromoethyl phosphonate **31.9**(Aldrich) and

potassium carbonate, to afford the amine **31.10**. The product is then with reacted one molar equivalent of carbonyldiimidazole in tetrahydrofuran, to give the imidazolide product **31.11**. The compound is then reacted with the tert. butyl ester of valine **31.12**, in pyridine at ambient temperature, to afford the carbamate product **31.13**. The tert. butyl ester is then removed by treatment of the ester **31.13** with trifluoroacetic acid at 0°, as described in J. Am. Chem. Soc., 99, 2353, 1977, to afford the carboxylic acid **31.14**.

Using the above procedures, but employing, in place of the benzyl alcohol derivative **31.8**, different benzyl alcohols **31.1**, and/or different bromo-substituted alkyl phosphonates **31.2**, the corresponding products **31.7** are obtained.

Scheme 32 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid **C4** (Chart 2a) in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol **32.1** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **32.2**. The coupling reaction between aryl bromides and olefins is described above (Scheme 11). The coupled product **32.3** is then converted into the carbamate derivative **32.5**, by means of the series of reactions illustrated above (Scheme 31) for the conversion of the benzyl alcohol **31.3** into the carbamate derivative **31.7**. Alternatively, the unsaturated compound **32.3** is reduced, diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.8, to produce the saturated analog **32.4**. This material is then transformed, as described above, into the carbamate derivative **32.6**.

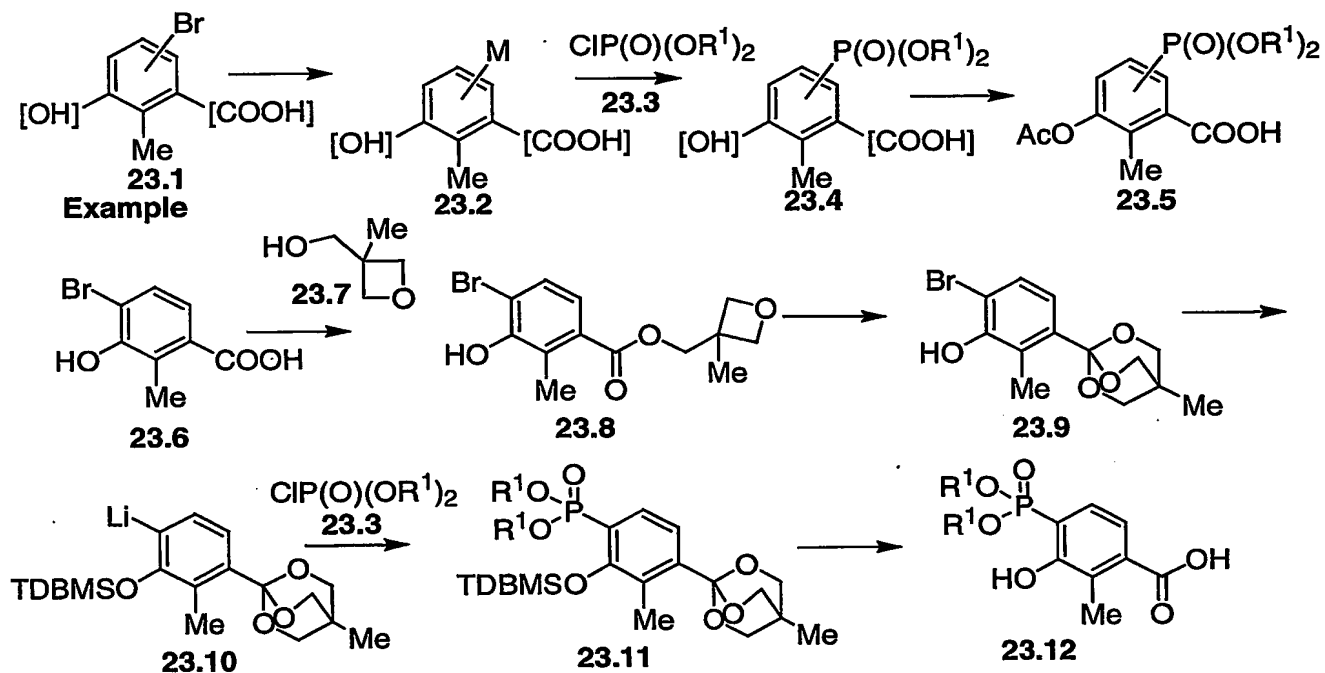
For example, 4-bromobenzyl alcohol **32.7** is coupled, in the presence of diethyl vinylphosphonate, prepared as described in Synthesis, 1983, 556, in the presence of ca. 3 mol % of palladium(II) acetate, triethylamine and tri(o-tolyl)phosphine in acetonitrile at ca. 100° in a sealed tube, as described in Synthesis, 1983, 556, to produce the coupled product **32.9**. The product is then converted, as described above, into the unsaturated and saturated carbamate derivatives **32.10** and **32.11**.

Using the above procedures, but employing, in place of 4-bromobenzyl alcohol **32.7**, different benzyl alcohols **32.1**, and/or different dialkyl alkenyl phosphonates **32.2**, the corresponding products **32.5** and **32.6** are obtained.

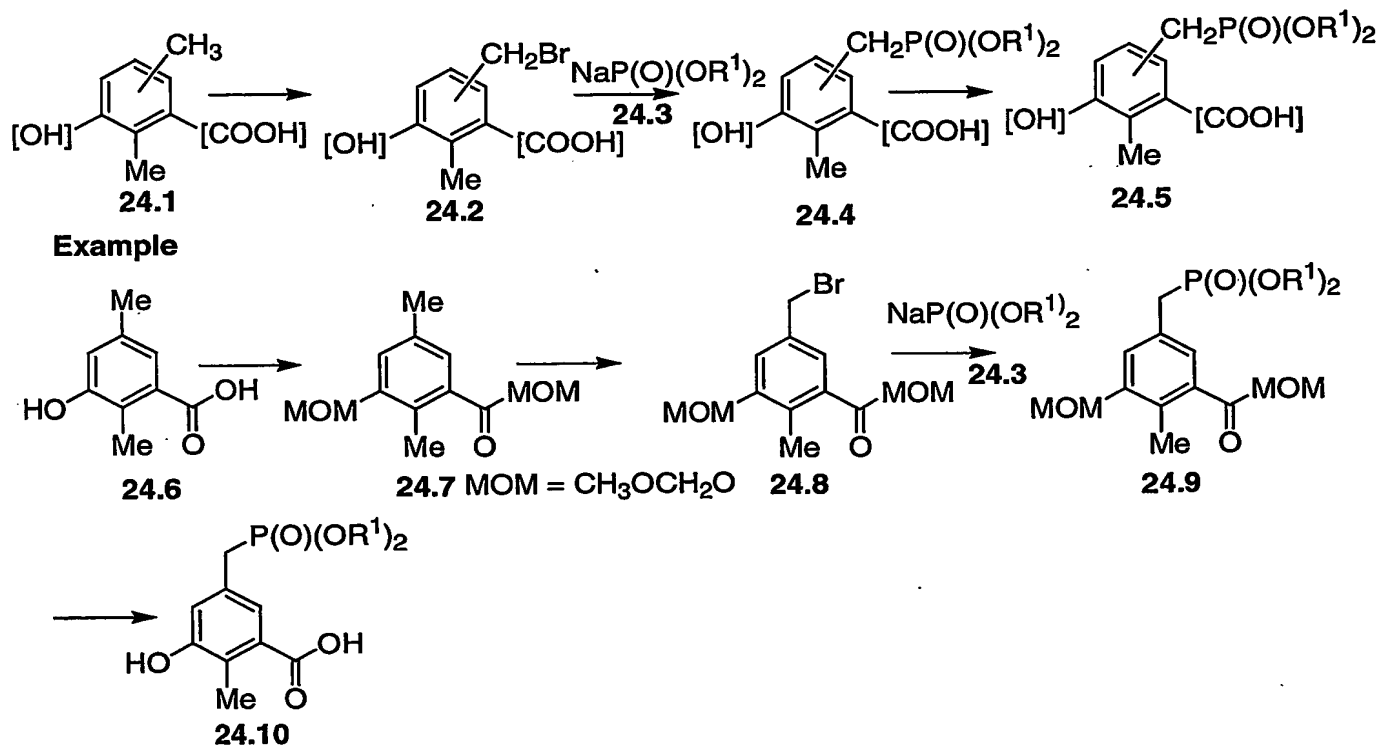
Scheme 33 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of a phenyl ring. In this procedure, a benzaldehyde boronic acid 33.1 is coupled, using the procedures described above (Scheme 27) with a dialkyl bromophenylphosphonate 33.2, to afford the biphenyl derivative 33.3. The aldehyde group is then reduced to give the corresponding benzyl alcohol 33.4. The reduction of aldehydes to afford alcohols is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968. The conversion can be effected by the use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diborane and the like. Preferably, the aldehyde 33.3 is reduced to the carbinol 33.4 by reaction with sodium borohydride in ethanol at ambient temperature. The resulting benzyl alcohol is then transformed, using the procedures described above, (Scheme 31) into the carbamate derivative 33.5.

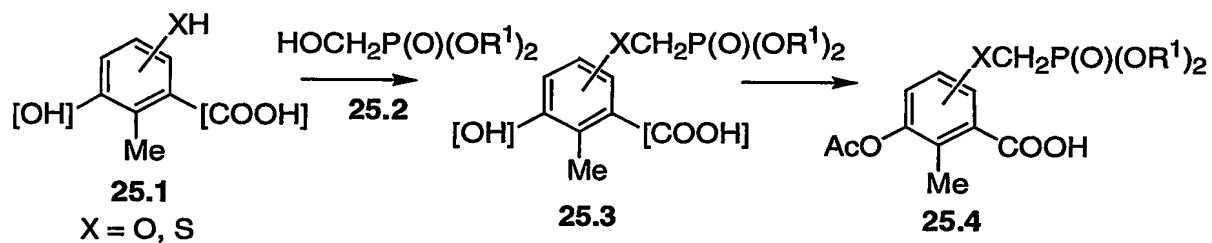
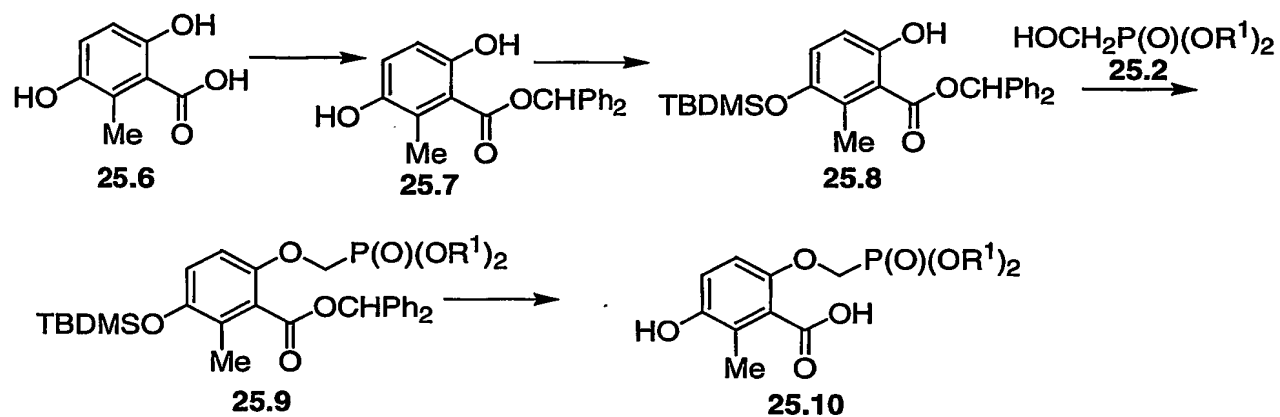
For example, 3-formylphenylboronic acid 33.6 (Fluka) is coupled with a dialkyl 4-bromophenylphosphonate 33.7, prepared as described in J. Organomet. Chem., 1999, 581, 62, in the presence of tetrakis(triphenylphosphine)palladium and sodium bicarbonate, as described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218, to yield the diphenyl compound 33.8. The aldehyde group is reduced to afford the carbinol 33.9, and the latter compound is then transformed, as described above, into the carbamate derivative 33.10. Using the above procedures, but employing, in place of the benzaldehyde 33.6, different benzaldehydes 33.1, and/or different dialkyl bromophenyl phosphonates 33.2, the corresponding products 33.4 are obtained.

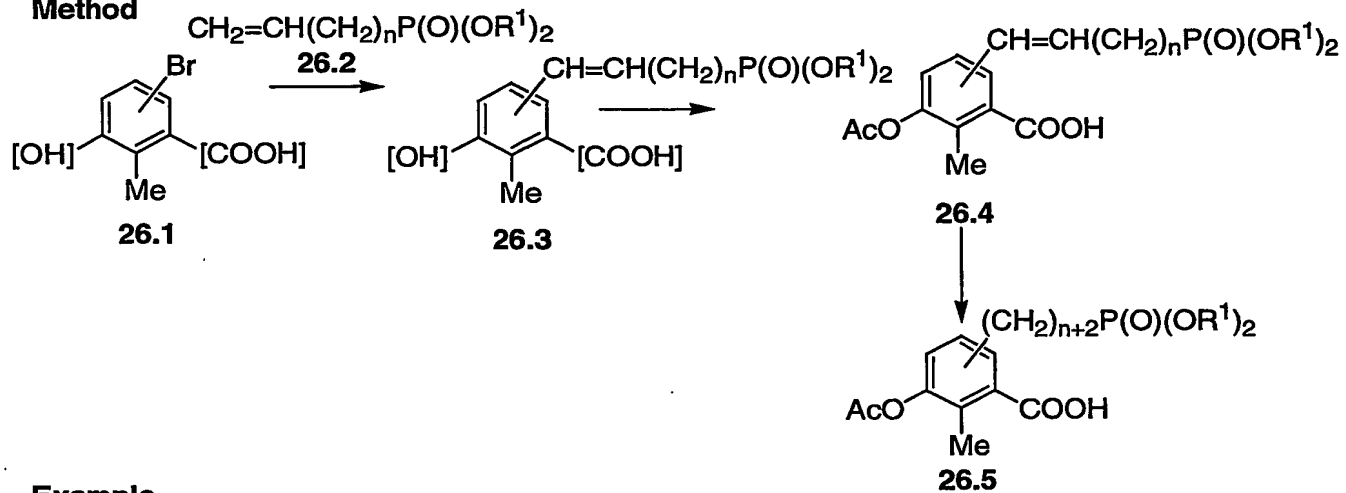
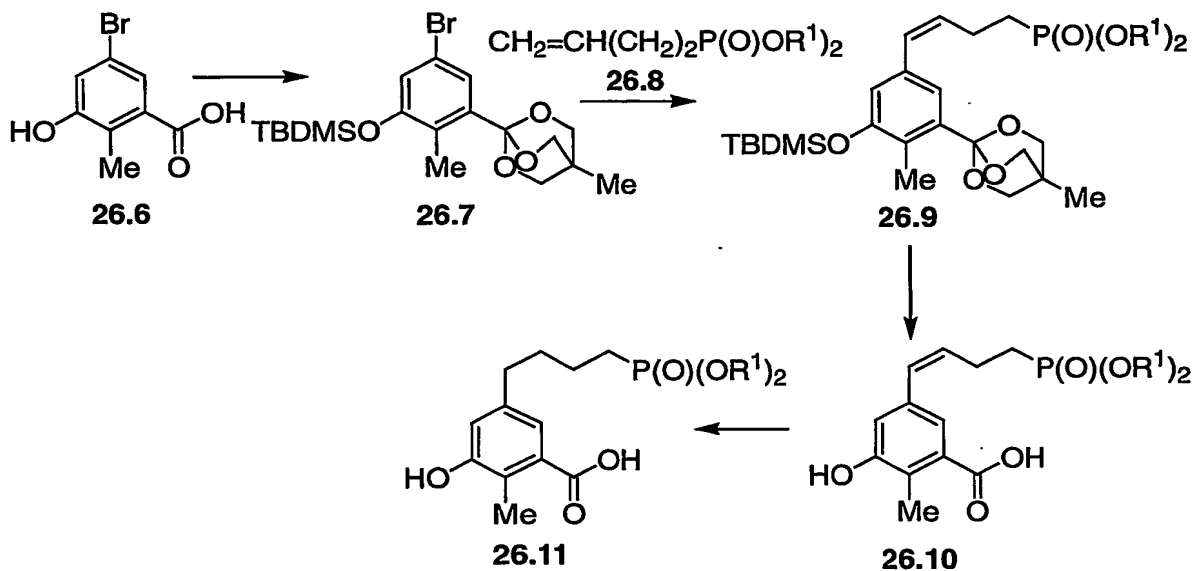
Scheme 23
Method

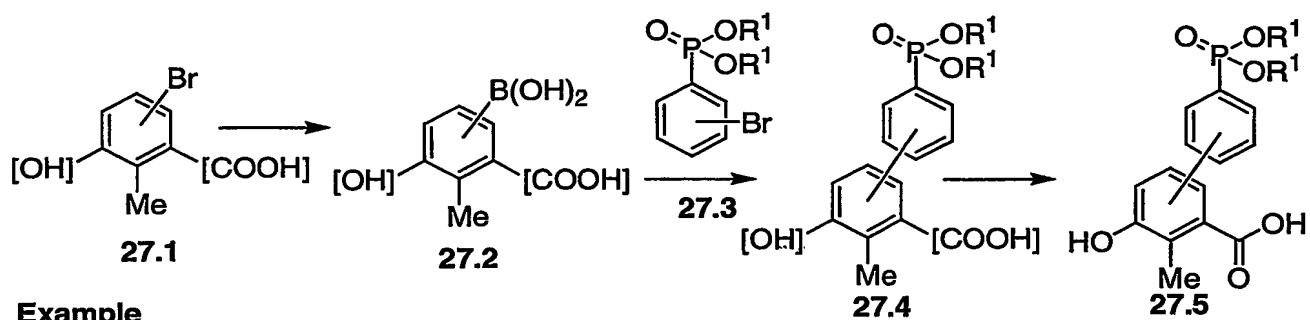
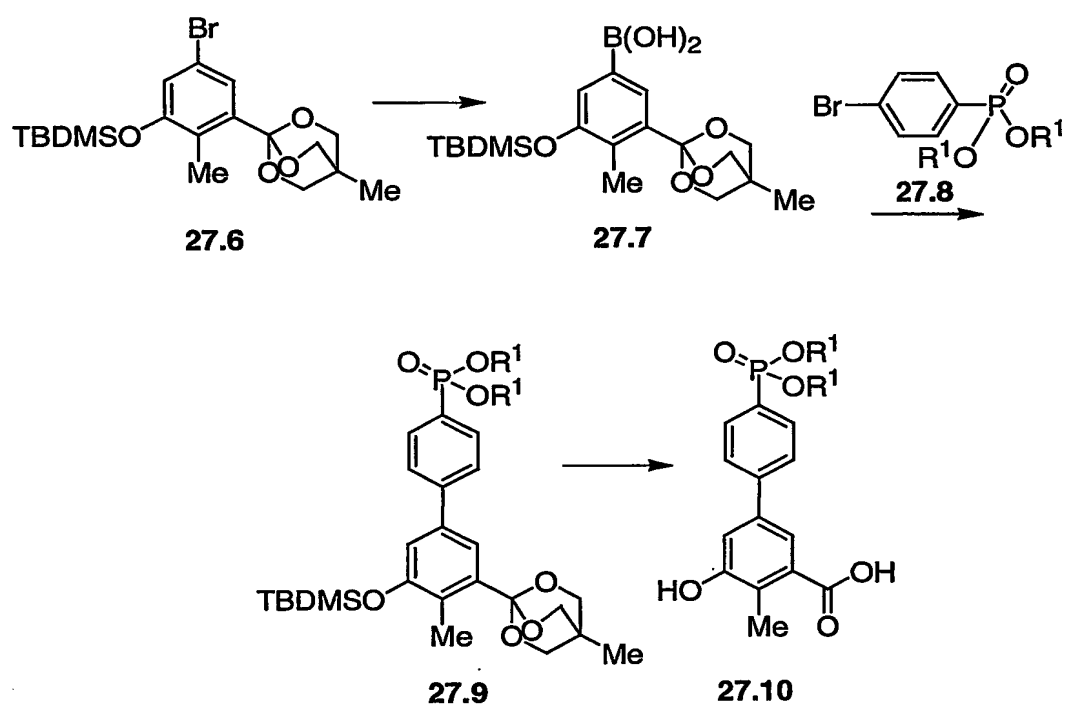


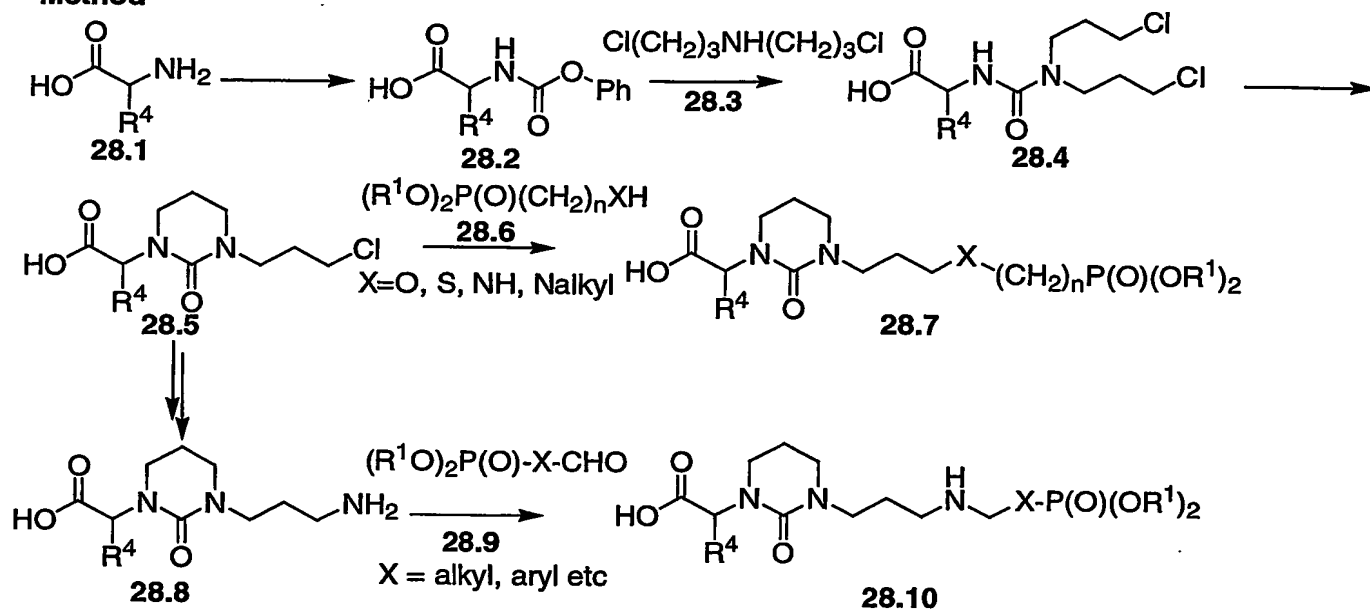
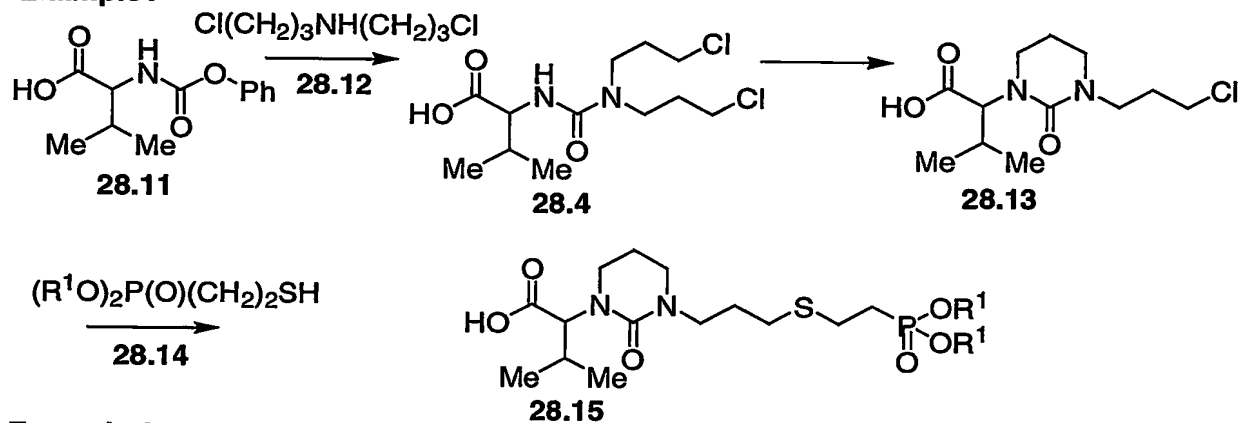
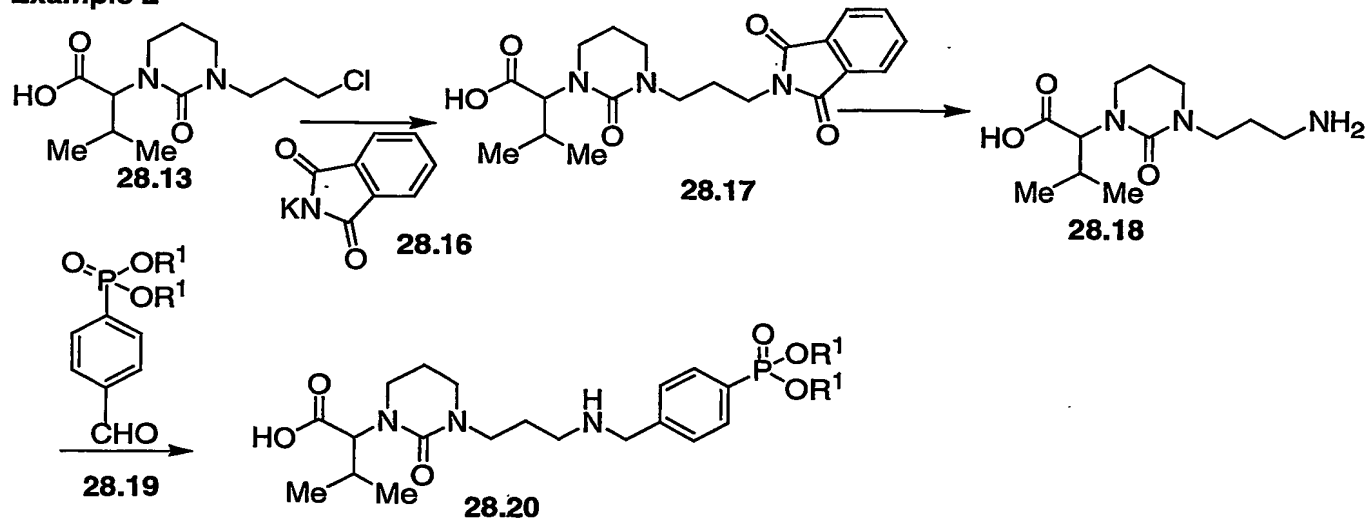
Scheme 24
Method

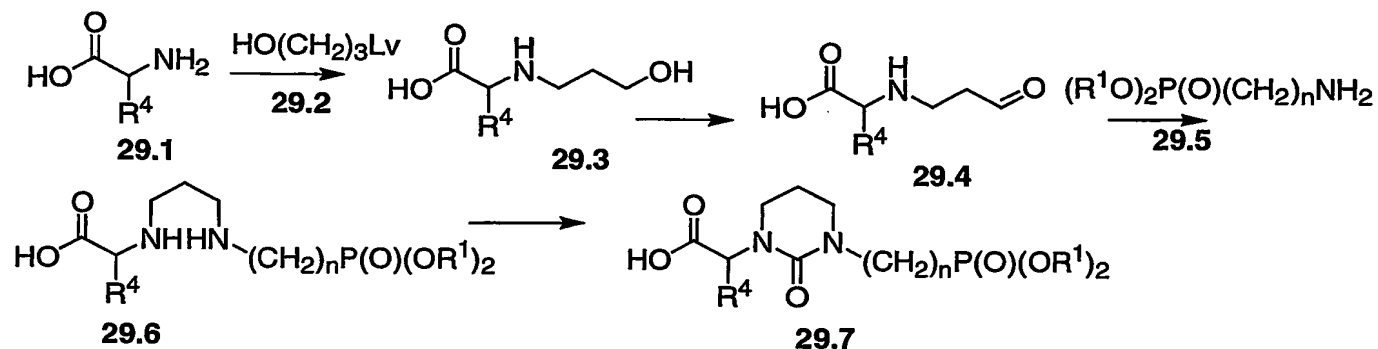
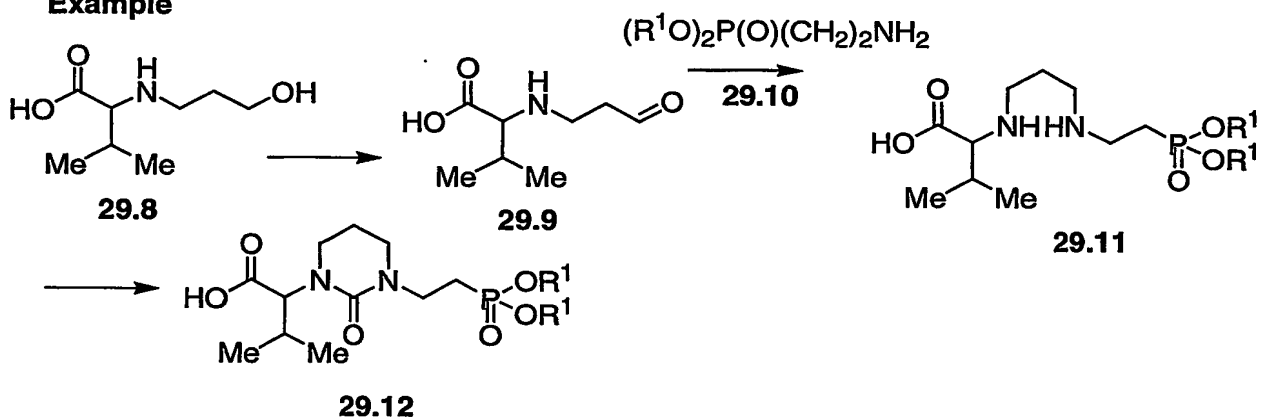
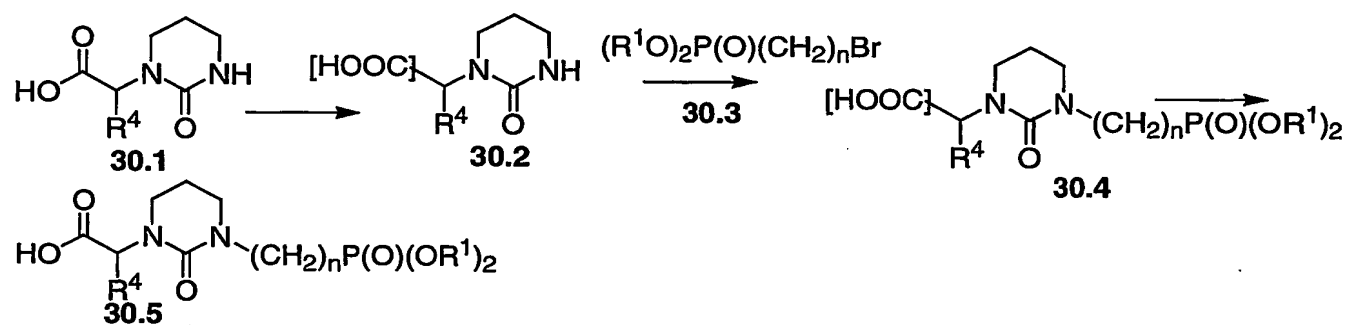
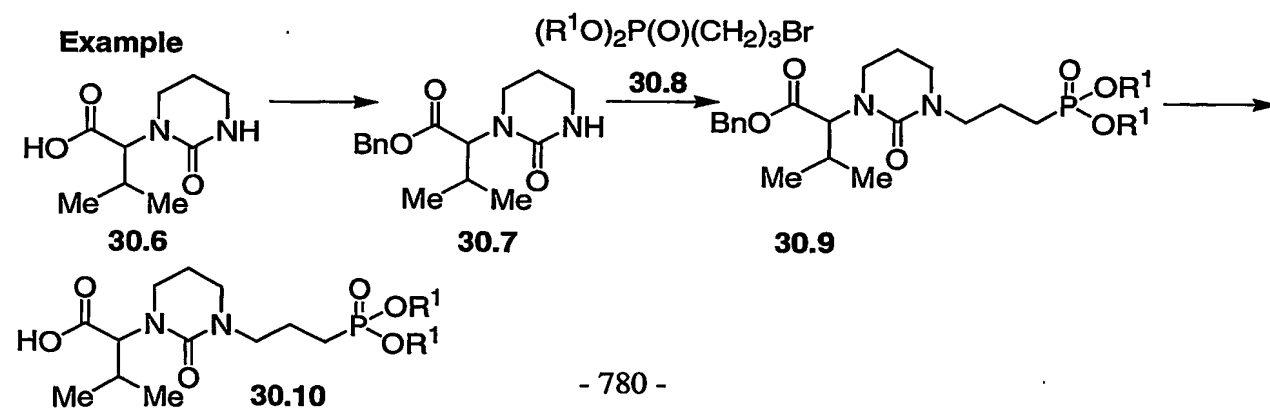


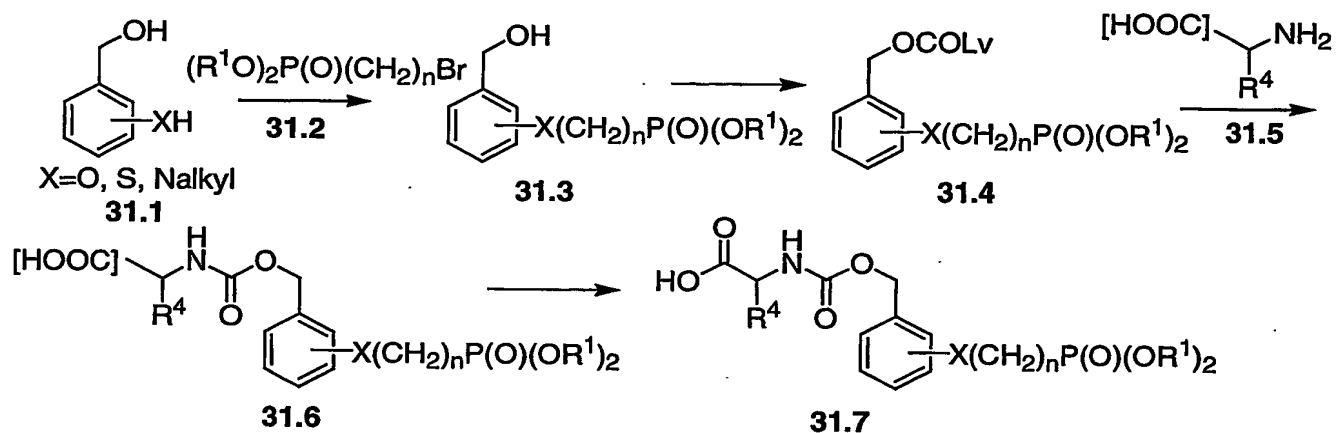
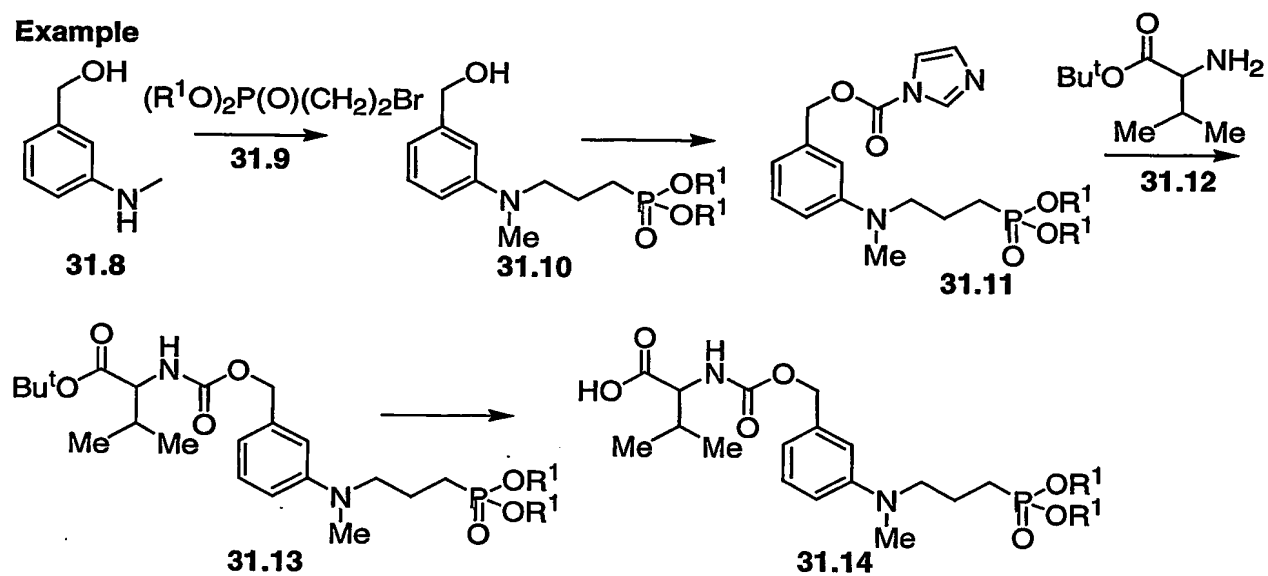
Scheme 25**Method****Example**

Scheme 26**Method****Example**

Scheme 27**Method****Example**

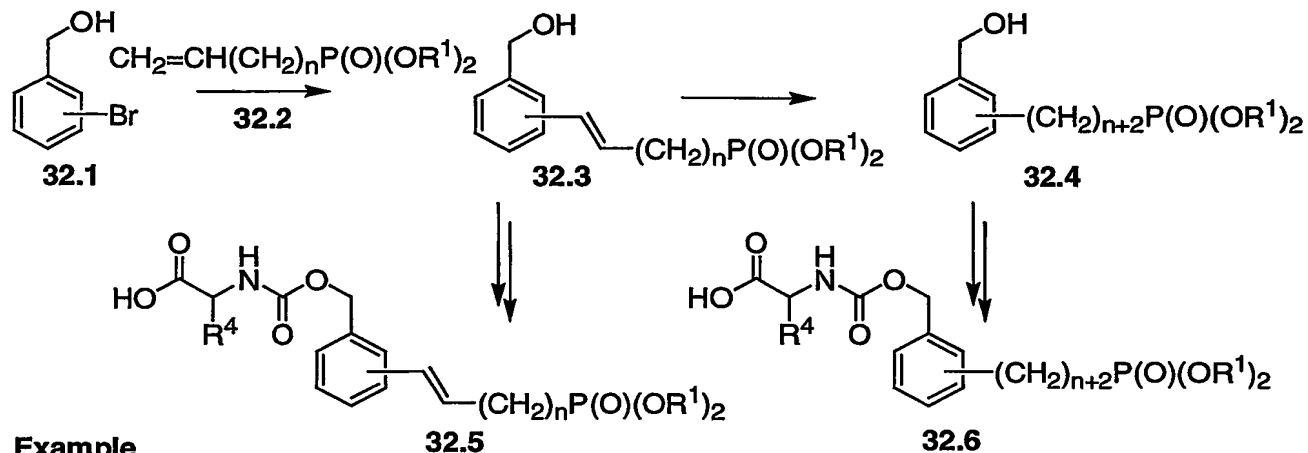
Scheme 28**Method****Example 1****Example 2**

Scheme 29**Method****Example****Scheme 30****Method****Example**

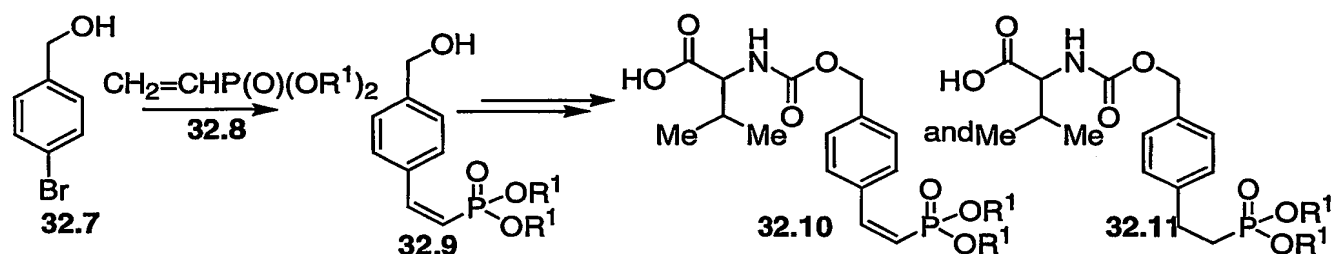
Scheme 31**Method****Example**

Scheme 32

Method

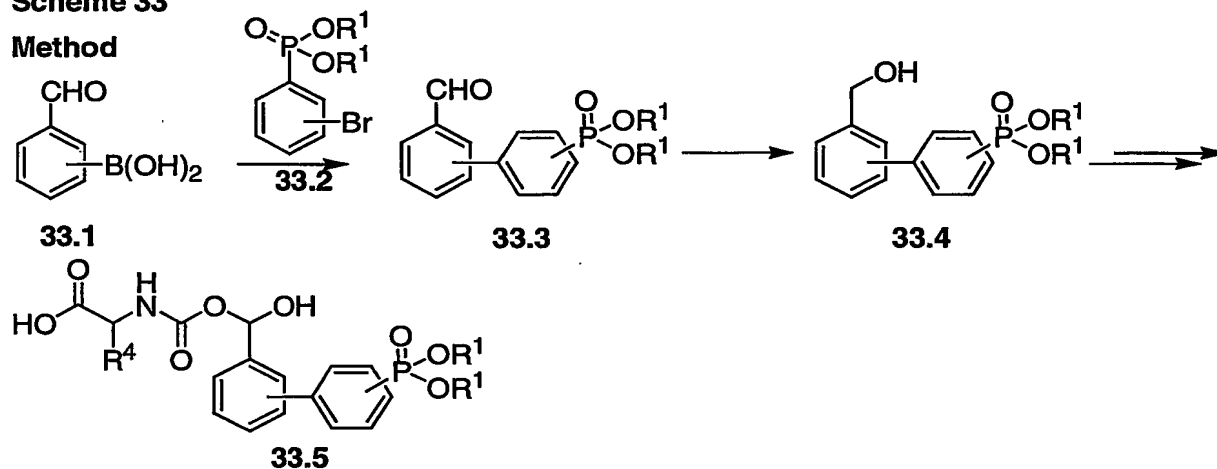


Example

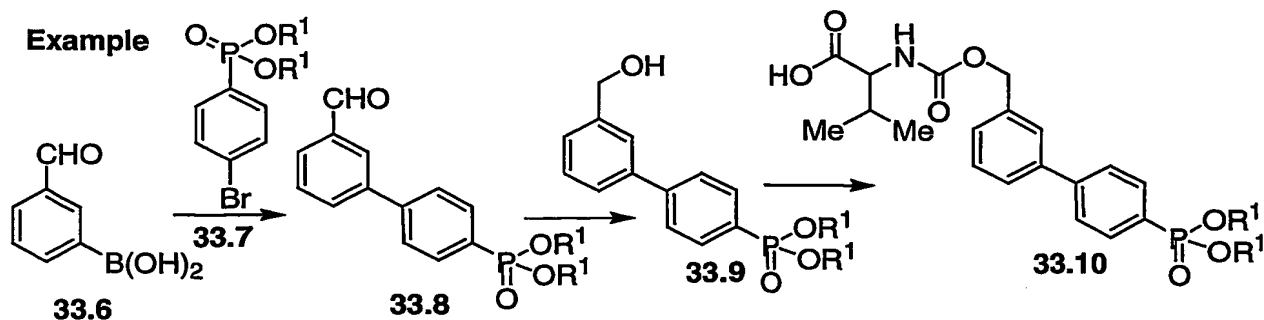


Scheme 33

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The methods described herein for the preparation of phosphonate ester intermediate compounds are, with appropriate modifications, generally applicable to different substrates, such as the carboxylic acids depicted in Charts 2a, 2b and 2c. Thus, the methods described above for the introduction of phosphonate groups into the dimethylphenoxyacetic acid moiety (Schemes 9-14), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine synthon for the preparation of the phosphonate esters 3. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes 15-17), the hydroxy methyl substituted benzoic acids (Schemes 23- 27), the tetrahydropyrimidine analogs (Schemes 28-30), and the benzyl carbamates (Schemes 31- 33) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the dimethylphenoxyacetic acid component.

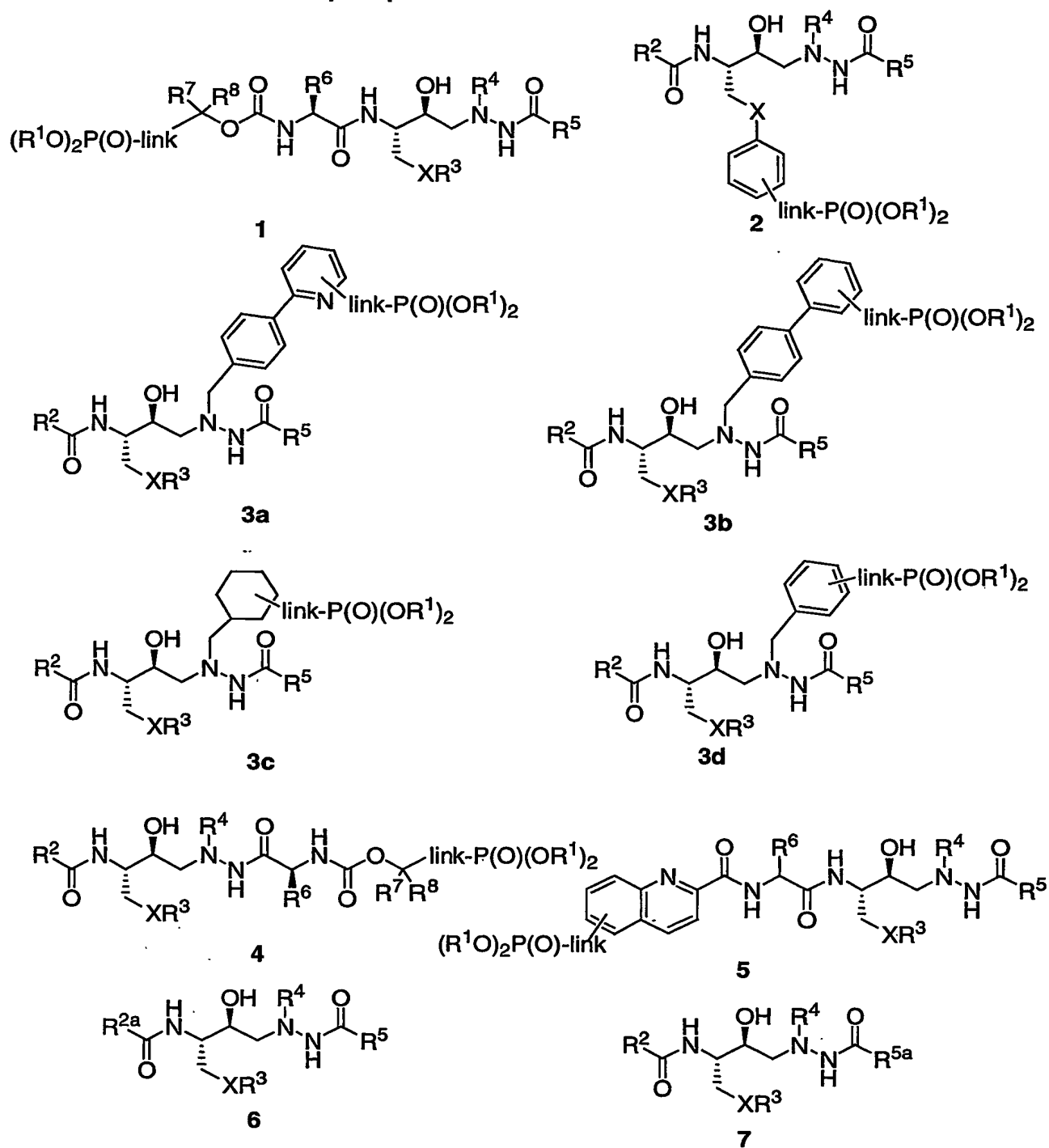
Atazanavir-like phosphonate protease inhibitors (ATLPPI)

Preparation of the intermediate phosphonate esters.

The structures of the intermediate phosphonate esters 1 to 7, and the structures for the component groups X, R¹, R⁷ and R⁸ of this invention are shown in Chart 1. The structures of the R²COOH and R⁵COOH components are shown in Charts 2a, 2b and 2c, and the structures of the R³XCH₂ components are shown in Chart 3. The structures of the R⁴ components are shown in Chart 4. Specific stereoisomers of some of the structures are shown in Charts 1-4; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 7. Subsequent chemical modifications to the compounds 1 to 7, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds 1 to 7 incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 5 and 6 illustrate examples of the linking groups present in the structures 1 - 7. The term "etc" in Charts 3, 5 and 6, refers to the scaffold atazanavir.

Schemes **1 - 56** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1- 5**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **6** and **7**, in which the phosphonate moiety is incorporated into the groups R^2COOH and R^5COOH , are also described below.

Chart 1. Structures of the phosphonate esters 1 - 7.

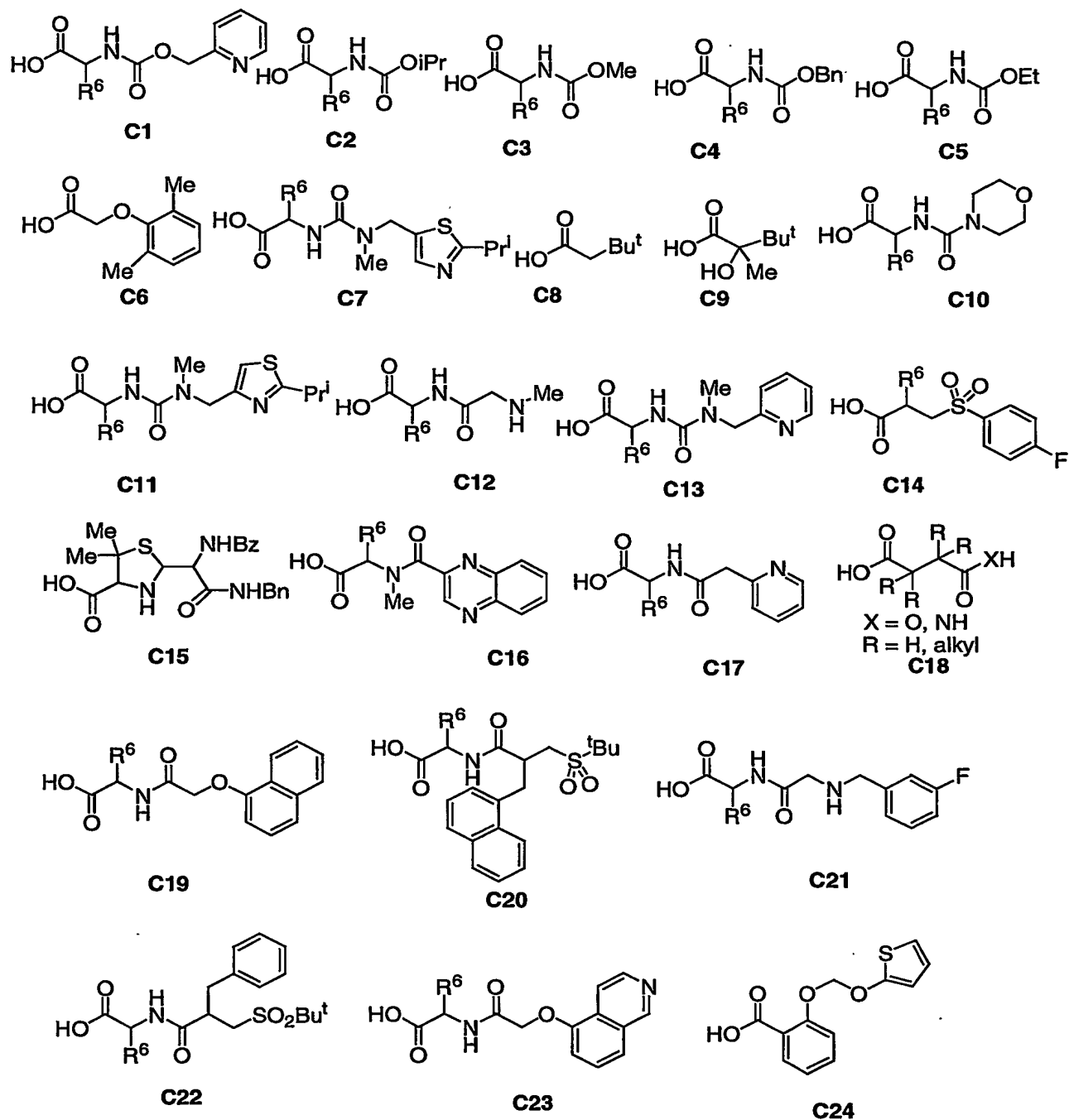
R^{2a} = phosphonate-containing R^2

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

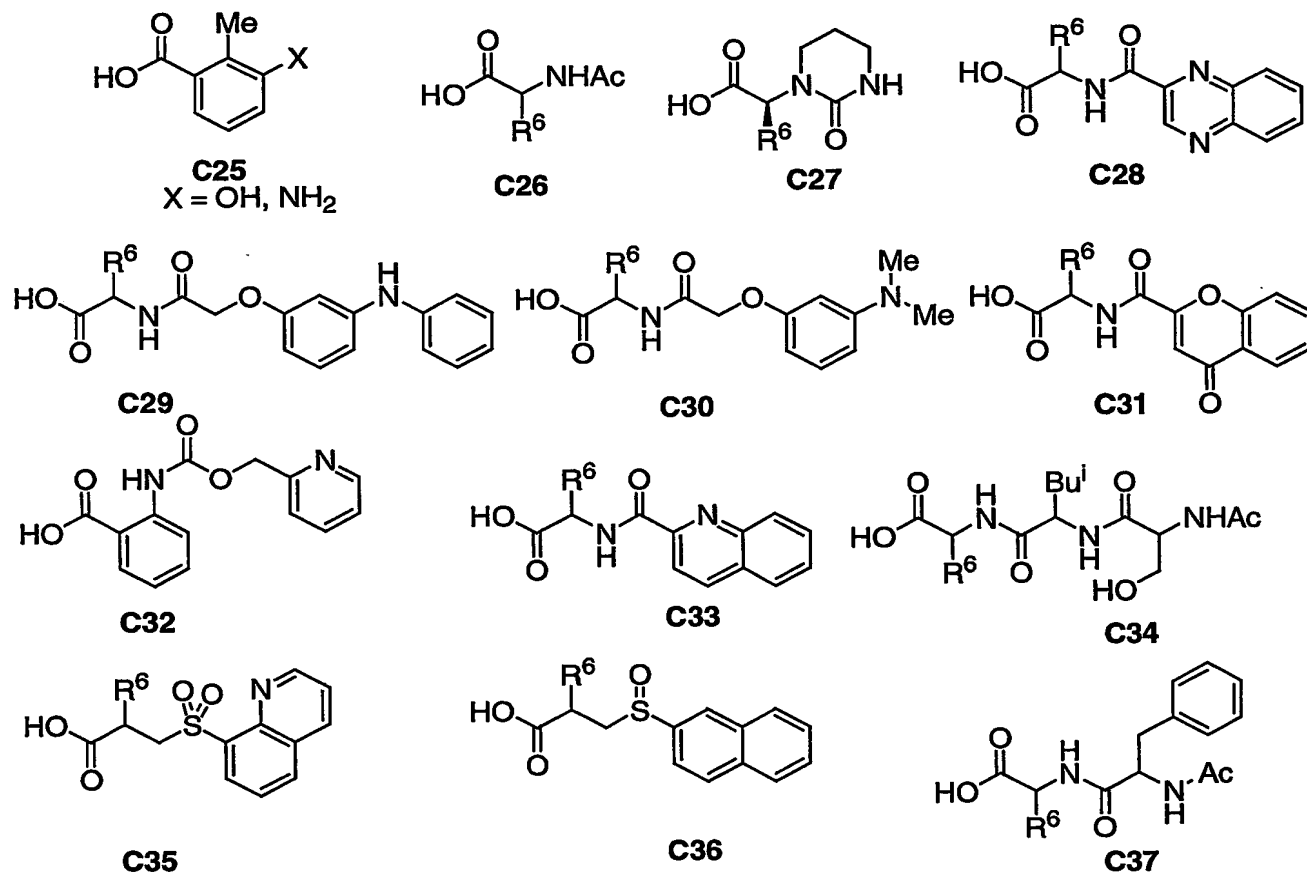
R^7, R^8 = H, alkyl

X = direct bond; sulfur.

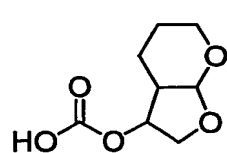
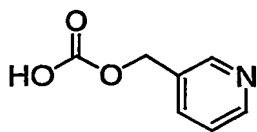
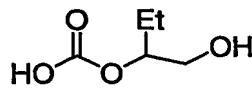
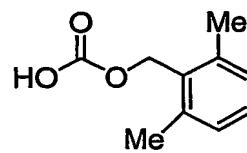
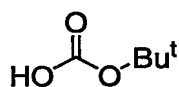
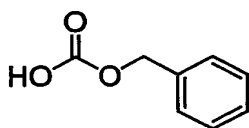
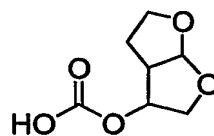
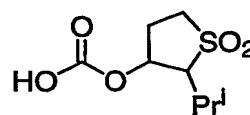
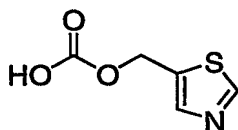
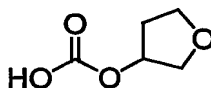
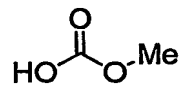
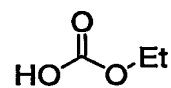
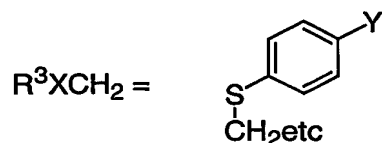
R^{5a} = phosphonate-containing R^5

Chart 2a Structures of the R²COOH and R⁵COOH components

R⁶ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl,
 CH₂NHAc, CH₂NHCOCF₃

Chart 2b Structures of the R²COOH and R⁵COOH components

R⁶ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, NHAc, NHCOCF₃

Chart 2c Structures of the R²COOH and R⁵COOH components**C38****C39****C40****C41****C42****C43****C44****C45****C46****C47****C48****C49****Chart 3 Structures of the R³XCH₂ groups.****8**

Y = H, F

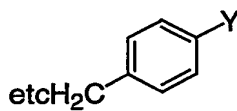
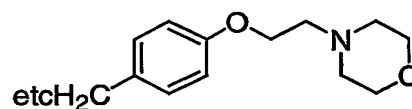
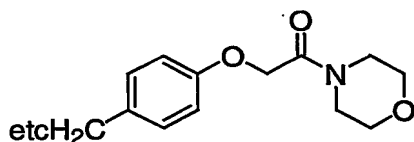
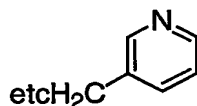
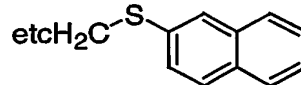
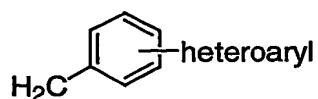
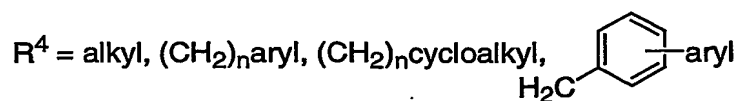
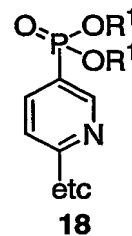
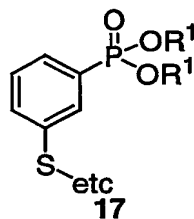
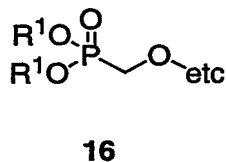
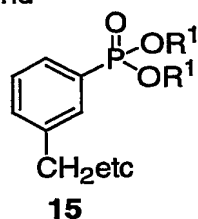
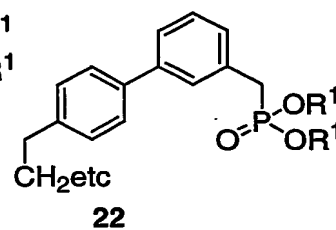
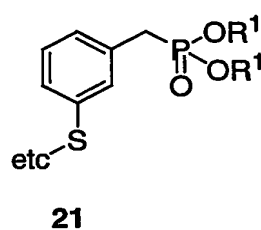
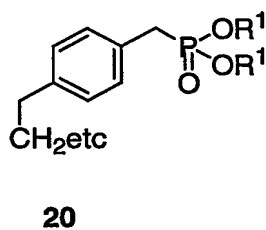
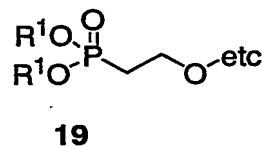
**9**Y = H, OC₂H₅, OCH₂C₆H₅**10****11****12****13****Chart 4 Structures of the R⁴ groups**

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.**link****examples**

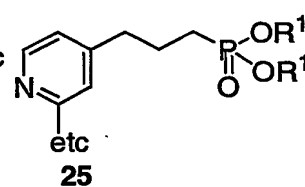
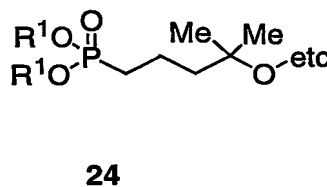
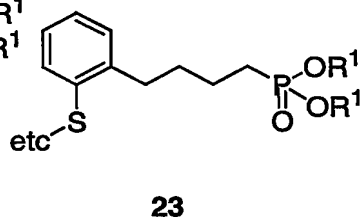
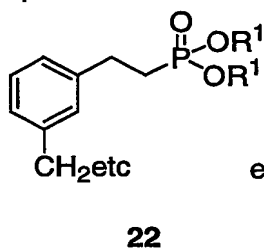
direct bond



single carbon



multiple carbon



hetero atoms

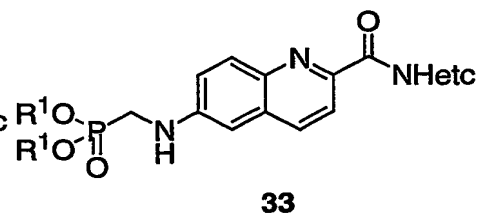
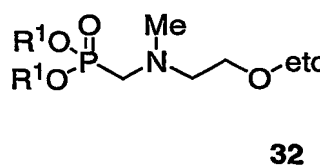
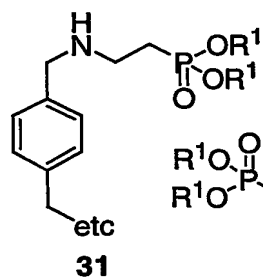
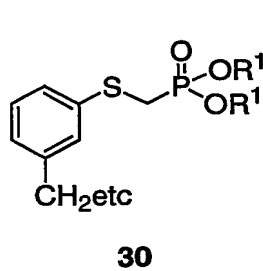
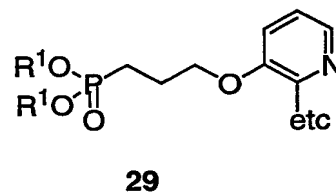
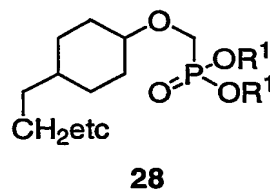
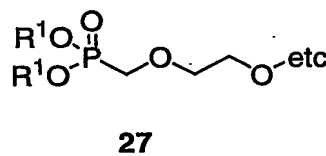
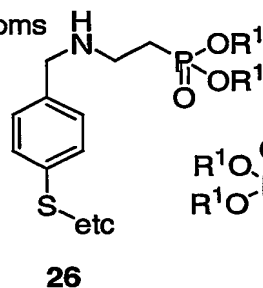
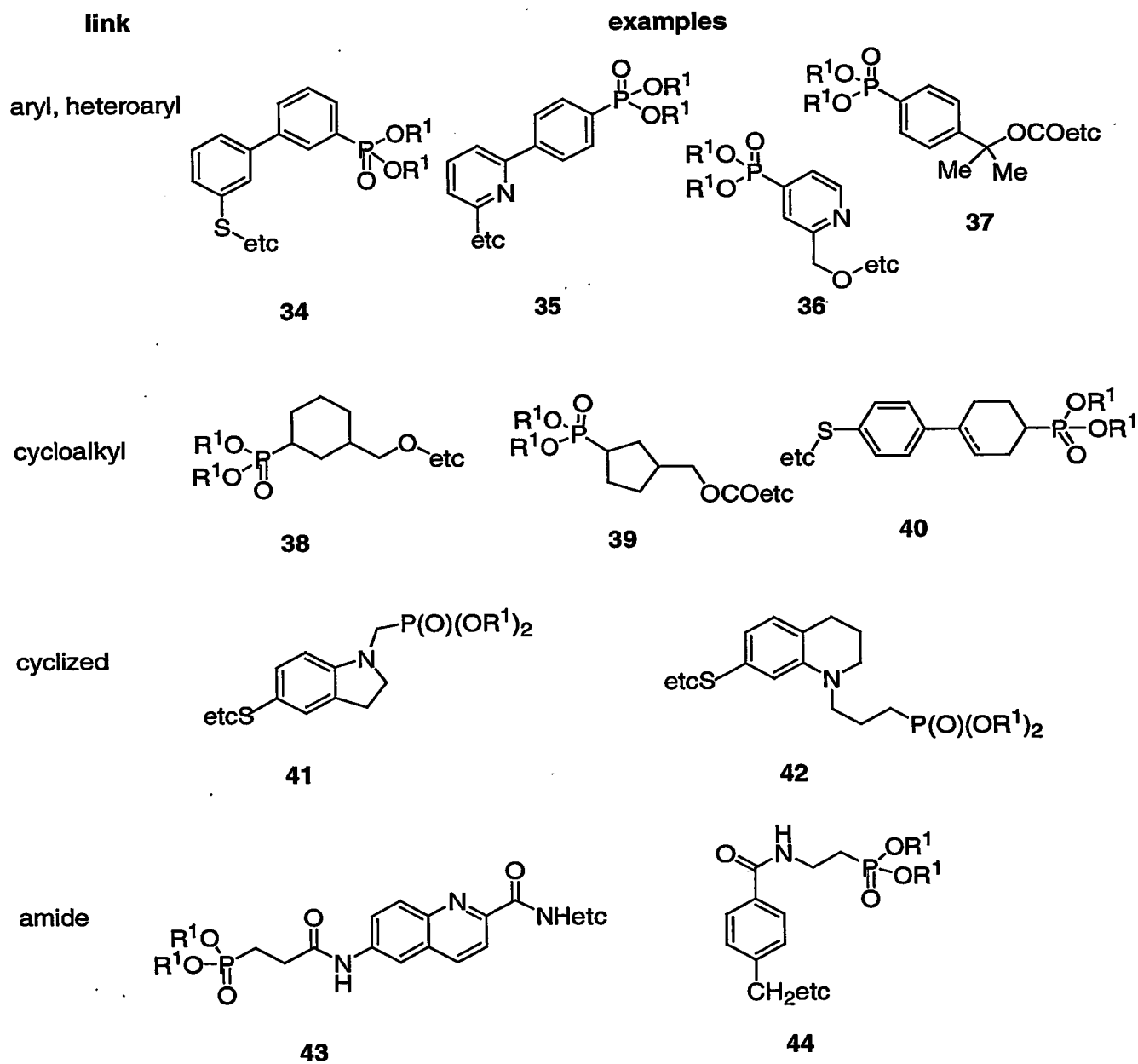


Chart 6 Examples of the linking group between the scaffold and the phosphonate moiety.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain
5 reactive substituents from unwanted reactions by protection before the sequence described,
and to deprotect the substituents afterwards, according to the knowledge of one skilled in the
art. Protection and deprotection of functional groups are described, for example, in Protective
Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.
Reactive substituents which may be protected are shown in the accompanying schemes as, for
10 example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes 1 and 2 illustrate the preparation of the phosphonate esters 1 in which X is a direct
15 bond. As shown in Scheme 1, the oxirane 1.1 is reacted with the BOC-protected hydrazine
derivative 1.2 to afford the aminoalcohol 1.3. The preparation of the oxiranes 1.1, in which Y
is as defined in Scheme 1, is described below, (Scheme 3). The preparation of the hydrazine
derivatives $R^4NHNHBOC$ is described below, (Scheme 4). The reaction between the oxirane
1.1 and the hydrazine 1.2 is conducted in a polar organic solvent such as dimethylformamide,
20 acetonitrile or, preferably, a lower alkanol. For example, equimolar amounts of the reactants
are combined in isopropanol and heated to ca. 80° for about 16 hours, as described in WO
9740029, to afford the aminoalcohol 1.3. The cbz protecting group is then removed from the
product to yield the free amine 1.4. The removal of carbobenzyloxy substituents to afford the
corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene
25 and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the
use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a
palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate
with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described
in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient
30 temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can
also be removed by treatment with a Lewis acid such as boron tribromide, as described in J.
Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Preferably, the protected amine **1.3** is converted into the free amine **1.4** by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438.

5 The amine product **1.4** is then reacted with a carboxylic acid **1.5** to afford the amide **1.6**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the
10 presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, imidazolid and the like, and then reacted with the amine, in the presence of
15 an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10° , in the presence
20 of dicyclohexylcarbodiimide, as described in U.S. Patent 5,196,438, to afford the aminoamide **1.6**. The aminoamide is then reacted with a reagent $A-CR^7R^8OCOX$ (**1.7**), in which the substituent A is the group $(R^1O)_2P(O)$ -link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate **1.8**. The reagent $A-CR^7R^8OCOX$ is derived from the corresponding alcohol $A-CR^7R^8OH$, using methods described below, (Scheme 20). The preparation of the reactants A-
25 CR^7R^8OCOX is described in Schemes 21 - 26. The preparation of carbamates by means of reactions between alcohols and amines is described in Scheme 20.

The BOC-protected amine present in the carbamate product **1.8** is then deprotected to produce the free amine **1.9**. The removal of BOC protecting groups is described, for example,
30 in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid or formic acid, or

by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **1.8** with hydrogen chloride in tetrahydrofuran, for example as described in *Org. Process Res. Dev.*, 2002, 6, 323. The resulting amine **1.9** is then coupled with a carboxylic acid or an activated derivative thereof **1.10**, to afford the amide

5 **1.11**, using the conditions described above for the preparation of the amide **1.6**.

For example, the amine **1.9** is reacted with the carboxylic acid **1.10**, X = OH, in the presence of a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydroxybenztriazole and triethylamine, as described in *J. Med. Chem.*, 41, 1988, 3387, to yield the amide **1.11**.

10 The procedures illustrated in Scheme 1 depict the preparation of the compounds **1.11** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH], Br, as described below. Scheme 2 illustrates the conversion of compounds **1.11** in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below,
15 (Schemes **21 - 56**). In the procedures illustrated above, (Scheme 1) and in the procedures illustrated below (Schemes **3 - 19**) for the preparation of the phosphonate esters **1 - 7**, compounds in which the group A is a precursor to the group link-P(O)(OR¹)₂ may be converted into compounds in which A is link-P(O)(OR¹)₂ at any appropriate stage in the reaction sequence, or, as shown in Scheme 2, at the end of the sequence. The selection of an
20 appropriate stage to effect the conversion of the group A into the group link-P(O)(OR¹)₂ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those reaction conditions.

Scheme 3 illustrates the preparation of the epoxides **1.1** used above in Scheme 1. The
25 preparation of the epoxide **1.1** in which R⁷ is H is described in *J. Org. Chem.*, 1994, 59, 3656. Analogs in which R⁷ is one of the substituents defined in Chart 3 are prepared as shown in Scheme 3. A substituted phenylalanine **3.1** is first converted into the benzyloxycarbonyl (cbz) derivative **3.2**. The preparation of benzyloxycarbonyl amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,
30 p. 335. The aminoacid **3.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **3.2**. The conversion of the carboxylic acid **3.2** into the epoxide **1.1**, for

example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, and in J. Org. Chem., 1994, 59, 3656 is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride **3.3**, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **3.4**. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°. The diazoketone **3.4** is converted into the chloroketone **3.5** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Org. Chem., 1994, 59, 3656. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°, to produce a mixture of chlorohydrins from which the minor diastereomer **3.6** is separated by chromatography. The chlorohydrin **3.6** is then converted into the epoxide **1.1** by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound **3.6** is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**. The preparations of analogs of the oxirane **1.1** in which the amino group is protected respectively as the tert-butoxycarbonyl and trifluoroacetyl derivatives are described respectively in J. Med. Chem., 1994, 37, 1758 and J. Med. Chem., 1996, 39, 3203.

Scheme 4 depicts the preparation of the hydrazine derivatives **1.2**, in which R⁴ is CH₂-aryl, CH₂-alkyl, CH₂-cycloalkyl as shown in Chart 4. The general procedure for the preparation of BOC-protected hydrazine derivatives from the corresponding aldehyde RCHO (**4.1**) is shown in Scheme 4. The aldehyde is reacted with tert. butyl carbazate **4.2**, in a solvent such as an alkanol, a hydrocarbon such as toluene, or a polar organic solvent such as dimethylformamide, to afford the substituted hydrazone **4.3**. Preferably, equimolar amounts of the reactants are heated in a mixture of toluene and isopropanol, as described in Org. Process Res. Dev., 2002, 6, 323, to prepare the hydrazone **4.3**. The product is then reduced to the corresponding hydrazine derivative **4.4**. The transformation can be effected by chemical reduction, for example by the use of sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride or the like, or by palladium-catalyzed reduction in the presence of hydrogen or a hydrogen donor such as ammonium formate. Preferably, the hydrazone **4.3**

is reduced to the hydrazine **4.4** by hydrogenation at ambient temperature and pressure, in the presence of palladium hydroxide on carbon, as described in Org. Process Res. Dev., 2002, 6, 323.

The preparation of the hydrazine derivatives **1.2** in which a diaryl moiety is present is shown in Scheme 4, Example 1. In this procedure, a formyl-substituted phenyl boronate **4.5** (Lancaster Synthesis) is transformed, by means of a palladium-catalyzed coupling with an aryl or heteroaryl bromide **4.6**, to afford the aldehyde **4.7**. The coupling of aryl bromides with aryl boronates is described, for example, in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218 and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 57. Typically, the reactants **4.5** and **4.6** are combined in an aprotic organic solvent such as dimethylformamide in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium and a base such as sodium bicarbonate or potassium acetate, to afford the coupled product **4.7**. This material is then reacted with a protected hydrazine derivative such as tert-butoxycarbonylhydrazine (tert-butyl carbazate) **4.2**, to yield the hydrazone **4.8**. The reaction between equimolar amounts of the aldehyde and the protected hydrazine is conducted in alcoholic solvent such as ethanol, at reflux temperature, for example as described in WO9740029, to produce the hydrazone **4.8**. The latter compound is then reduced, for example by the use of hydrogen in the presence of a palladium catalyst, as described in WO 9740029, or by the use of sodium cyanoborohydride and p-toluenesulfonic acid in tetrahydrofuran, as described in J. Med. Chem., 1998, 41, 3387, to afford the substituted hydrazine **1.2**. Other reactants **1.2**, in which R⁴ is as defined in Chart 4, are prepared from the appropriate aldehydes, using the procedures of Scheme 4.

Scheme 4, Example 2 illustrates the preparation of phosphonate-containing pyridylphenyl hydrazine derivatives **4.11**, which are employed in the preparation of the phosphonate esters **3a**. In this procedure, a phosphonate-substituted pyridyl benzaldehyde **4.9**, the preparation of which is described below, (Schemes 40 and 41) is reacted, as described above, with tert. butyl carbazate **4.2**, to afford the hydrazone **4.10**. This compound is then reduced, in the presence of palladium hydroxide as catalyst, as described above, to yield the hydrazine product **4.11**.

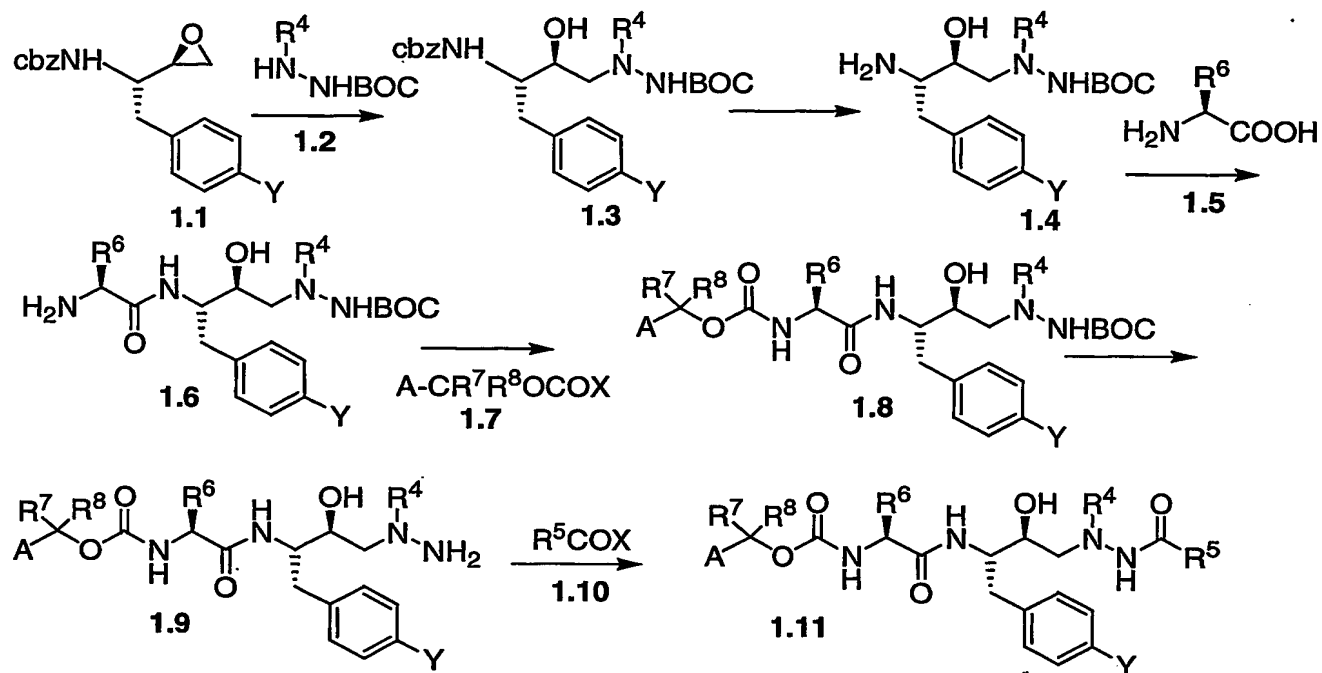
Scheme 4, Example 3 illustrates the preparation of phosphonate-containing biphenyl hydrazine derivatives **4.13**, which are employed in the preparation of the phosphonate esters **3b**. In this procedure, a phosphonate-substituted phenyl benzaldehyde **4.12** the preparation of which is

described below, (Schemes 42- 44) is converted, as described above in Example 2 into hydrazine product 4.13.

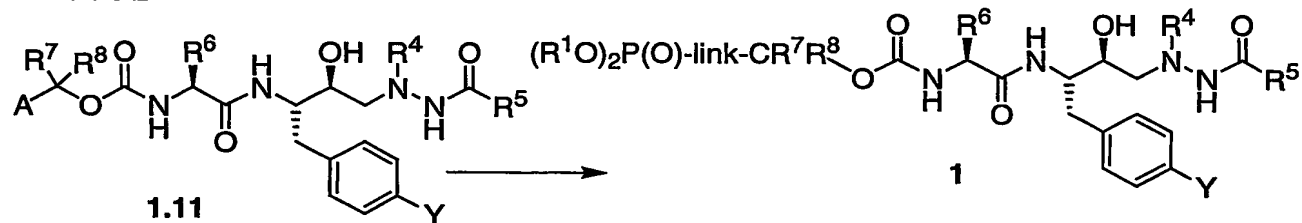
Scheme 4, Example 4 illustrates the preparation of phosphonate-containing phenyl hydrazine derivatives 4.15, which are employed in the preparation of the phosphonate esters 3d. In this
5 procedure, a phosphonate-substituted phenyl benzaldehyde 4.14, the preparation of which is described below, (Schemes 45 - 48) is converted, as described above in Example 2 into hydrazine product 4.15.

Scheme 4, Example 5 illustrates the preparation of phosphonate-containing cyclohexyl hydrazine derivatives 4.17, which are employed in the preparation of the phosphonate esters
10 3c. In this procedure, a phosphonate-substituted cyclohexane carboxaldehyde 4.16, the preparation of which is described below, (Schemes 49 – 52) is converted, as described above in Example 2 into hydrazine product 4.17.

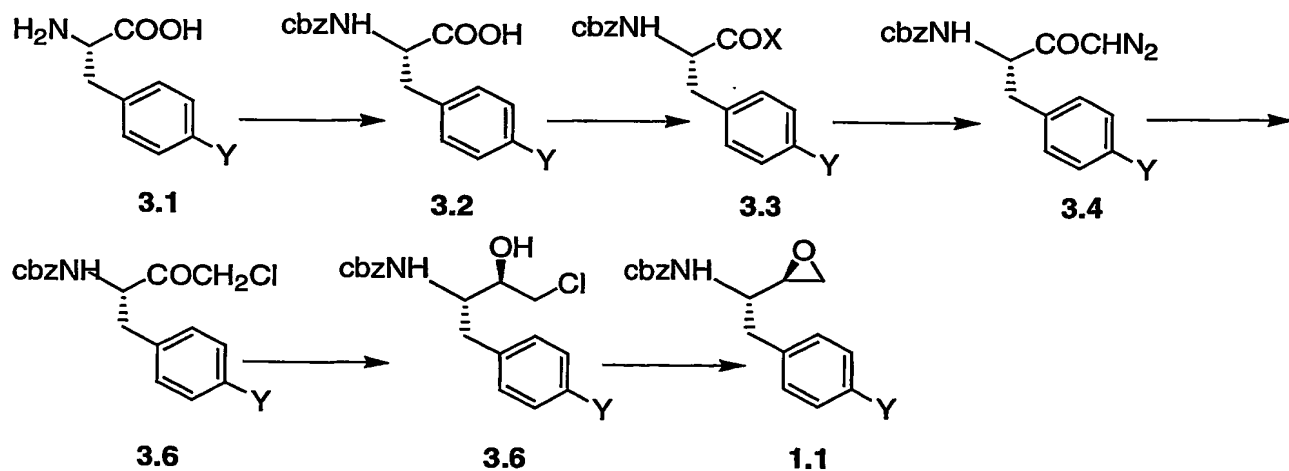
Scheme 1



Scheme 2



Scheme 3

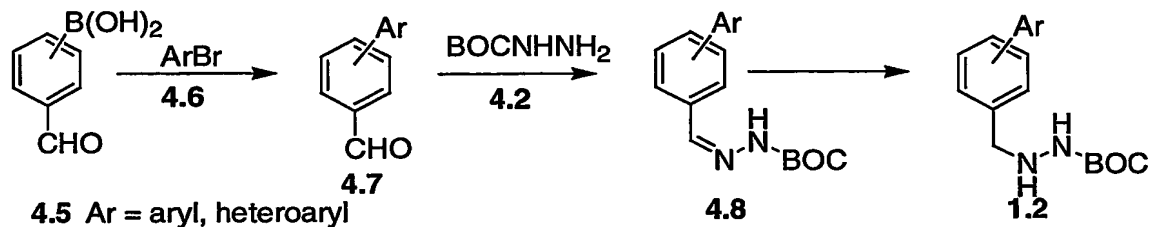


Scheme 4

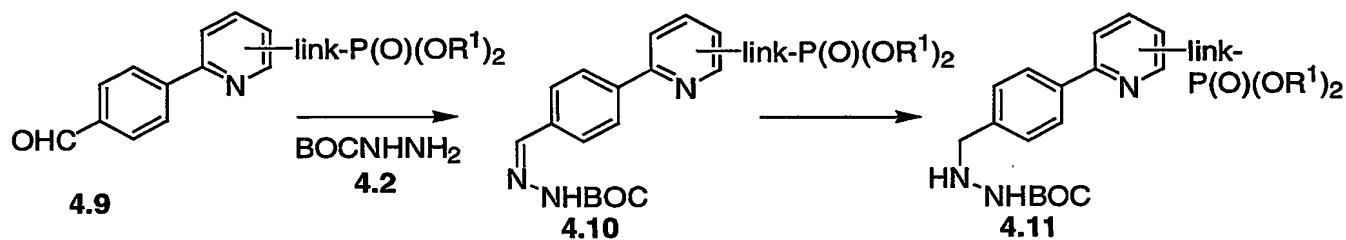
General reaction



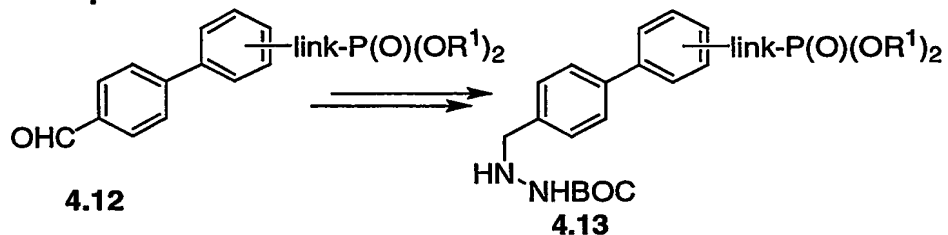
Example 1



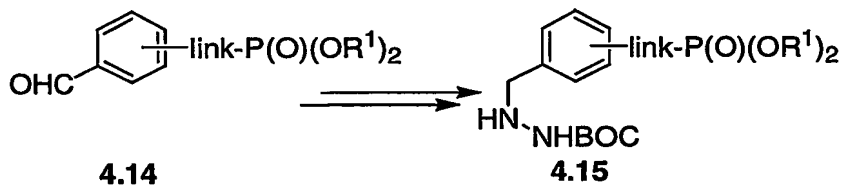
Example 2



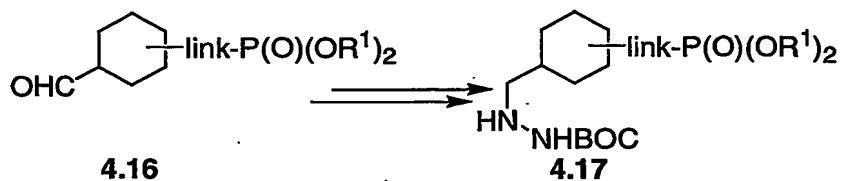
Example 3



Example 4



Example 5



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes 5 and 6 illustrate the preparation of the compounds 1 in which X is sulfur. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **5.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^3SH **5.2**, as defined above, to afford the thioether **5.3**.

The reaction is conducted in an organic solvent such as, for example, pyridine, DMF, toluene and the like, optionally in the presence of water, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours. Preferably the mesylate **5.1** is reacted with an equimolar amount of the thiol R^3SH **5.2**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, as described in J. Org. Chem., 1994, 59, 3656, to give the product **5.3**. The 1,3-dioxolane protecting group present in the compound **5.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **5.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound **5.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **5.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the diol product **5.4**.

The primary hydroxyl group of the diol **5.4** is then selectively activated by reaction with an electron-withdrawing reagent such as, for example, dinitrobenzoyl chloride or p-toluenesulfonyl chloride. The reaction is conducted in an inert solvent such as pyridine, dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **5.4** and p-toluenesulfonyl chloride are reacted in a solvent such as pyridine, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, as described in J. Org. Chem, 2000, 65, 1623, to afford the p-toluenesulfonate ester **5.5**.

The latter compound is then reacted with the hydrazine derivative **1.2** to afford the hydrazine **5.6**. The displacement reaction is conducted in a polar aprotic solvent such as

dimethylformamide, acetonitrile, dioxan and the like, in the presence of an organic or inorganic base, to afford the product **5.6**. Preferably, equimolar amounts of the reactants are combined in dimethylformamide at ca. 80° in the presence of potassium carbonate, to produce the hydrazine product **5.6**. The cbz protecting group is then removed to afford the amine **5.7**. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can also be removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979. Preferably, the cbz protecting group is removed by hydrogenation of the substrate **5.6** in the presence of 5% palladium on carbon catalyst, to yield the amine **5.7**. The amine is then coupled with the aminoacid **5.8** to give the amine **5.9**. The reaction is effected under the same conditions as described above for the preparation of the amide **1.6**.

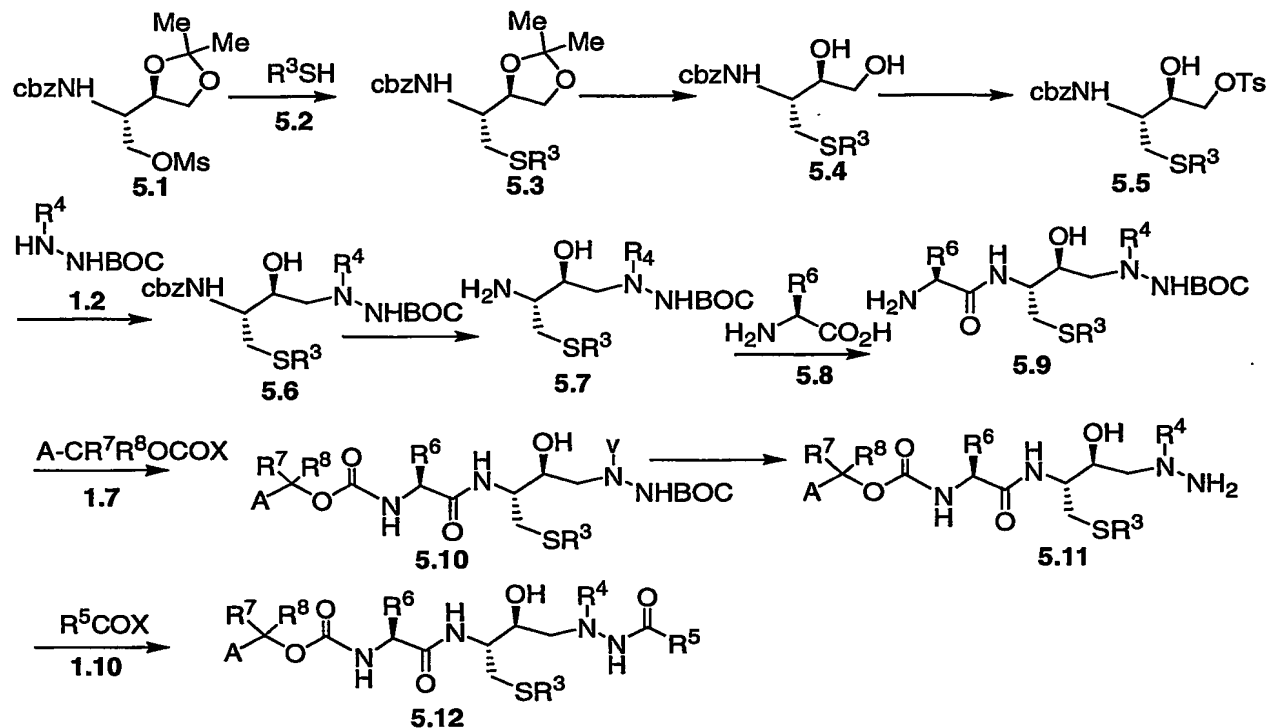
The amine is then reacted with a reagent $A-CR^7R^8OCOX$ (**1.7**), in which the substituent A is the group $(R^1O)_2P(O)$ -link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate **5.10**. The reagent $A-CR^7R^8OCOX$ is derived from the corresponding alcohol $A-CR^7R^8OH$, using methods described below, (Scheme 20). The preparation of the reactants $A-CR^7R^8OCOX$ is described in Schemes 21 - 26. The preparation of carbamates by means of reactions between alcohols and amines is described below, in Scheme 20.

The BOC protecting group is then removed from the product **5.10** to produce the hydrazine **5.11**. The conditions for the removal of the BOC group are the same as those described above (Scheme 1). The product is then acylated with the carboxylic acid or activated derivative thereof, **1.10**, using the conditions described above, (Scheme 1) to yield the product **5.12**.

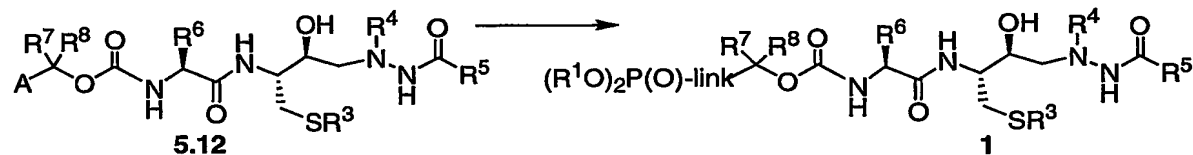
The procedures illustrated in Scheme 5 depict the preparation of the compounds **5.11** in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 6 illustrates the conversion of compounds **5.12** in which

A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 1. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

Scheme 5



Scheme 6



Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

- 10 Schemes 7 and 8 illustrate the preparation of the phosphonate esters 2 in which X is a direct bond. As shown in Scheme 7, a cbz-protected oxirane 7.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, is reacted with a hydrazine derivative 1.2, to afford the ring-opened product 7.3. The conditions for the reaction are the same as those described above for the preparation of the hydrazine derivative

1.3, (Scheme 1). The preparation of the substituted oxiranes 7.1 are described below, in Scheme 9. The product 7.3 is then transformed, using the sequence of reactions illustrated in Scheme 7, into the product 7.8. The conditions employed for the component reactions of this sequence are the same as for the analogous reaction in Scheme 1.

5

The procedures illustrated in Scheme 7 depict the preparation of the compounds 7.8 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 8 illustrates the conversion of compounds 7.8 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

10

Scheme 9 illustrates the preparation of the oxiranes 7.1. In this sequence, a substituted phenylalanine 9.1, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below, is transformed into the cbz-protected derivative 9.2, using the conditions described above for the preparation of the cbz derivative 3.2, (Scheme 3). The latter compound is then transformed, using the sequence of reactions illustrated in Scheme 3, into the product 7.1. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 3.

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Preparation of the phosphonate ester intermediates 2 in which X is a sulfur.

Schemes 10 and 11 illustrate the preparation of the compounds 2 in which X is sulfur. As shown in Scheme 10, the mesylate 5.1 is reacted with the substituted thiophenol 10.1, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below (scheme 30-39), to afford the thioether 10.2. The conditions employed for this reaction are the same as those described above for the preparation of the thioether 5.3, Scheme 5. The product 10.2 is then transformed, using the series of reactions shown in Scheme 5, into the diacylated thioether 10.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5.

25

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The procedures illustrated in Scheme 10 depict the preparation of the compounds 10.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as

[OH], [SH] Br, as described below. Scheme 11 illustrates the conversion of compounds 10.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

5

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes 12 and 13 depict the preparation of the phosphonate esters 3a in which X is a direct bond. As shown in Scheme 12, the oxirane 1.1 is reacted with a BOC protected
10 phenylhydrazine derivative 12.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. The preparation of the hydrazine derivatives 12.1 is described in Schemes 4, 40 and 41. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine 7.3, Scheme 7. The product 12.2 is then transformed, using the sequence of reactions shown in Scheme 7
15 for the transformation of the hydrazine 7.3 into the diacylated compound 7.8, into the diacylated compound 12.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 7.

The procedures illustrated in Scheme 12 depict the preparation of the phosphonate esters 12.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as
20 [OH], [SH] Br, as described below. Scheme 13 illustrates the conversion of compounds 12.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 3a in which X is a direct bond. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

The phosphonate esters 3b, 3c and 3d, in which X is a direct bond, are prepared using the
25 procedures of Schemes 12 and 13, except that the hydrazine derivatives 4.13, 4.17 and 4.15, prepared as described in Schemes 42 - 52, are used in place of the hydrazine derivative 12.1.

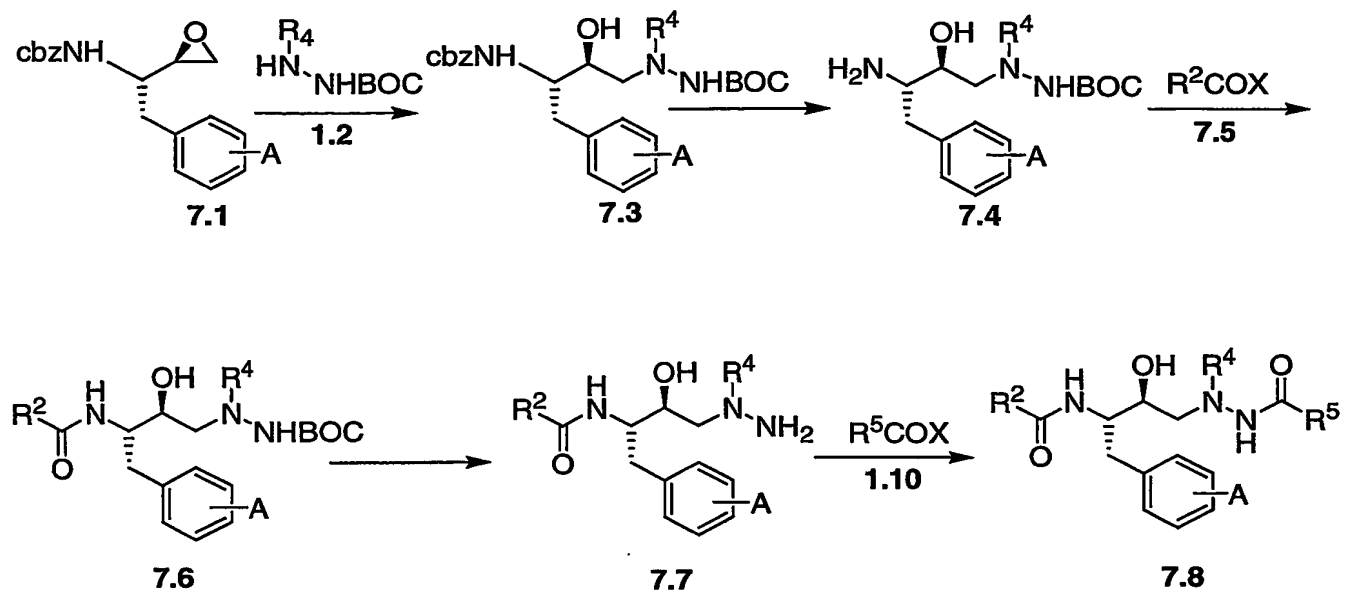
Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

Schemes 14 and 15 illustrate the preparation of the phosphonate esters **3a** in which X is sulfur.

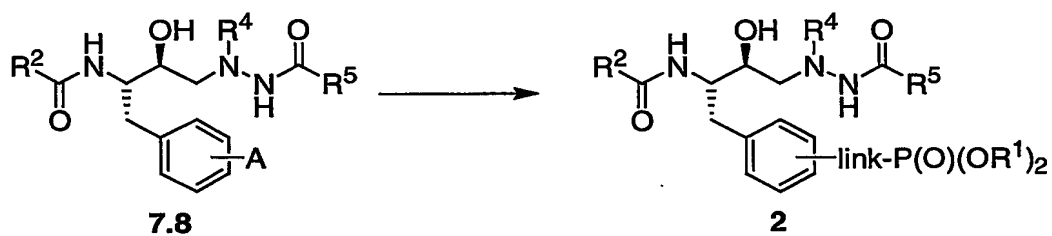
- 5 As shown in Scheme 14, the p-toluenesulfonate ester **5.5** is reacted with the phenylhydrazine derivative **12.1**, in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the hydrazine derivative **14.1**. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine **5.6**, Scheme 5. The product **14.1** is then transformed into the diacylated
- 10 product **14.2**, using the sequence of reactions shown in Scheme 5. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5. The procedures illustrated in Scheme 14 depict the preparation of the phosphonate esters **14.2** in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 15 illustrates the conversion of compounds **14.2**
- 15 in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds **3a** in which X is S. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 21 - 56).

- The phosphonate esters **3b**, **3c** and **3d**, in which X is S, are prepared using the procedures of Schemes 12 and 13, except that the hydrazine derivatives **4.13**, **4.17** and **4.15**, prepared as
- 20 described in Schemes 42 - 52, are used in place of the hydrazine derivative **12.1**.

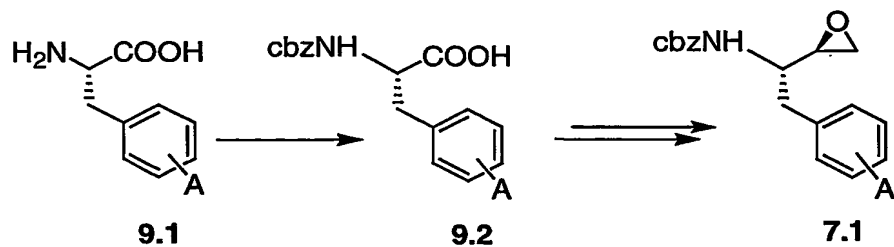
Scheme 7



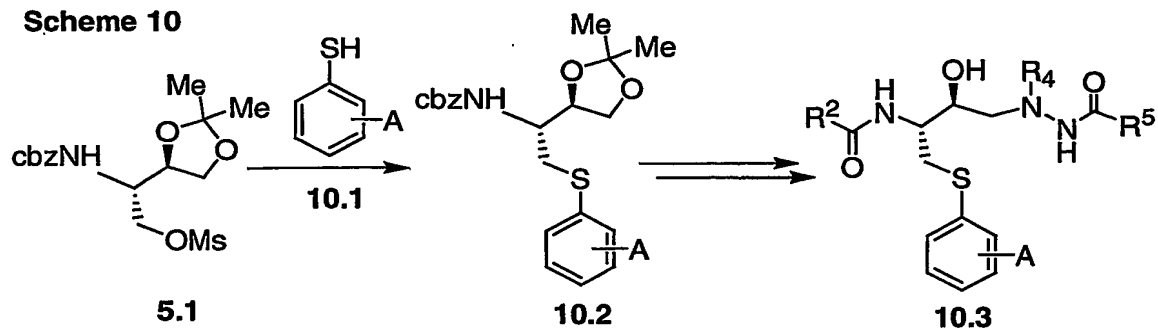
Scheme 8



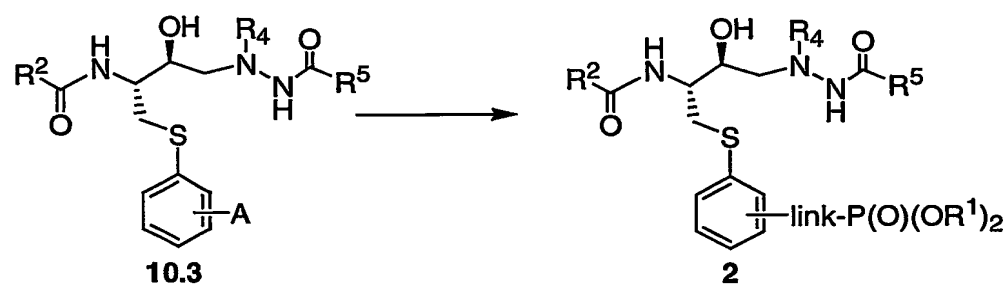
Scheme 9



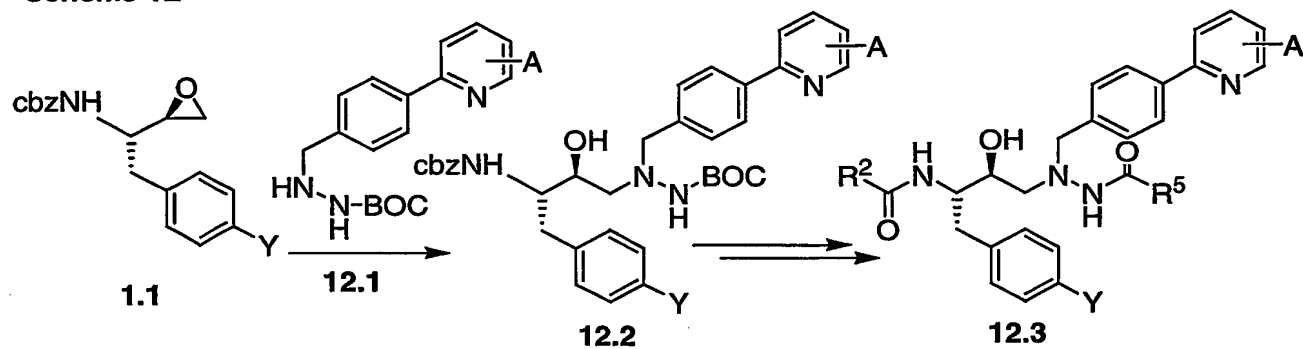
Scheme 10



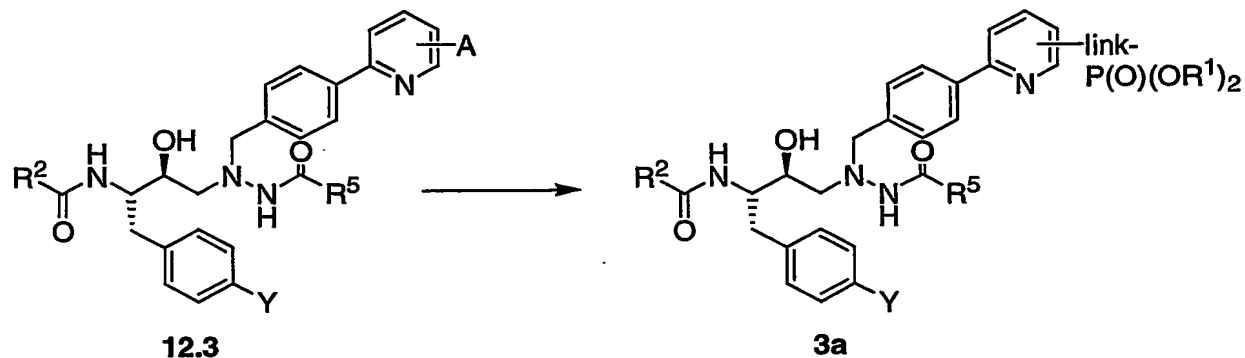
Scheme 11



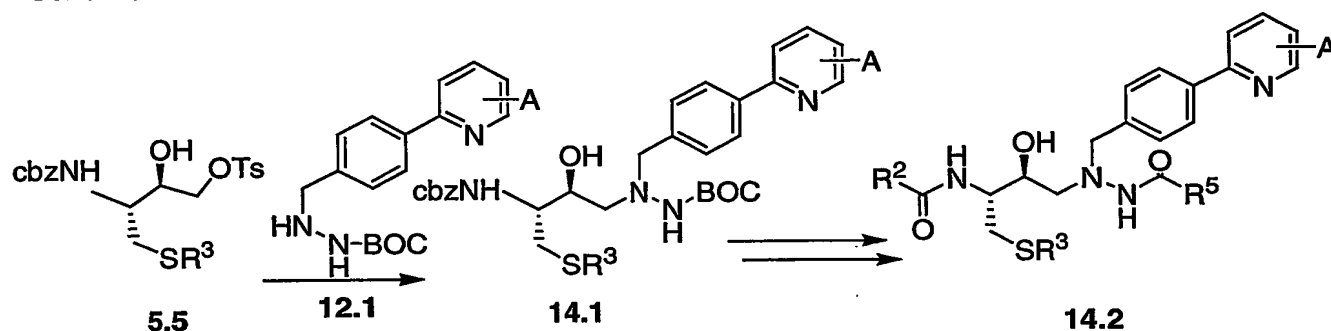
Scheme 12



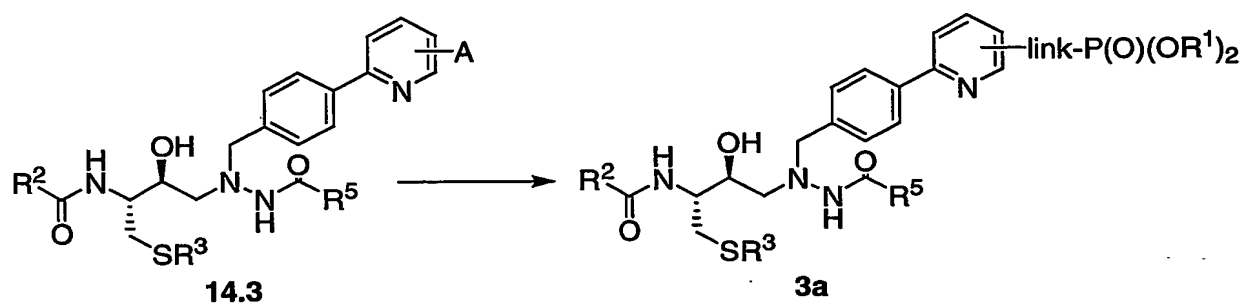
Scheme 13



Scheme 14



Scheme 15



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

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Schemes 16 and 17 illustrate the preparation of the phosphonate esters **4** in which X is a direct bond. As shown in Scheme 16, the amine **1.4**, prepared as described in Scheme 1, is reacted with the carboxylic acid or activated derivative thereof R²COX **7.5**, to afford the amide **16.1**. The conditions for the amide forming reaction are the same as those described above for the

preparation of the amide **1.11**, (Scheme 1). The product is then deprotected by removal of the BOC group, using the procedures described above (Scheme 1), to yield the hydrazine **16.2**.

This material is then coupled with the aminoacid **1.5**, using the coupling procedures described above for the preparation of the amide **1.6**, to produce the amide **16.3**. The product is then
5 reacted with the acylating agent A-CR⁷R⁸OCOX, **1.7**, in which A and X are as described above, Scheme 1, to afford the carbamate product **16.4**.

The procedures illustrated in Scheme 16 depict the preparation of the phosphonate esters **16.4** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 17 illustrates the conversion of compounds **16.4**
10 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 4. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes 18 and 19 illustrate the preparation of the phosphonate esters 4 in which X is sulfur. As shown in Scheme 18, the amine **5.7**, prepared as described in Scheme 5, is reacted with the carboxylic acid or activated derivative thereof **7.5**, to produce the amide **18.1**. The reaction is performed under the conditions described above for the preparation of the amide **1.11**. The
20 BOC group present in the amide **18.1** is then removed using the procedures described above, (Scheme 1) to afford the amine **18.2**. This material is then coupled with the aminoacid **1.5**, using the procedures described above for the preparation of the amide **1.6**, to produce the amide **18.3**. The latter compound is then reacted with the acylating agent A-CR⁷R⁸OCOX, **1.7**, in which A and X are as described above, Scheme 1, to afford the carbamate product
25 **18.4**.

The procedures illustrated in Scheme 18 depict the preparation of the phosphonate esters **18.4** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19 illustrates the conversion of compounds **18.4** in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 4. Procedures for
30 the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes 19a and 19b illustrate the preparation of the phosphonate esters 5 in which X is a direct bond. As shown in Scheme 19a, the amine 1.6 is reacted with a quinoline-2-carboxylic acid derivative 19a.1, in which the substituent A is either the group $(R^1O)_2P(O)$ -link or a precursor group thereto, such as OH, SH, Br to afford the amide 19a.2. The reaction is performed as described above for the preparation of the amide 1.6 (Scheme 1). The BOC protecting group is then removed, using the procedures described in Scheme 1, to yield the amine 19a.3. This compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19a.5.

The procedures illustrated in Scheme 19a depict the preparation of the phosphonate esters 19a.5 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19b illustrates the conversion of compounds 19a.5 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents 19a.1 is described below, (Schemes 53 - 56).

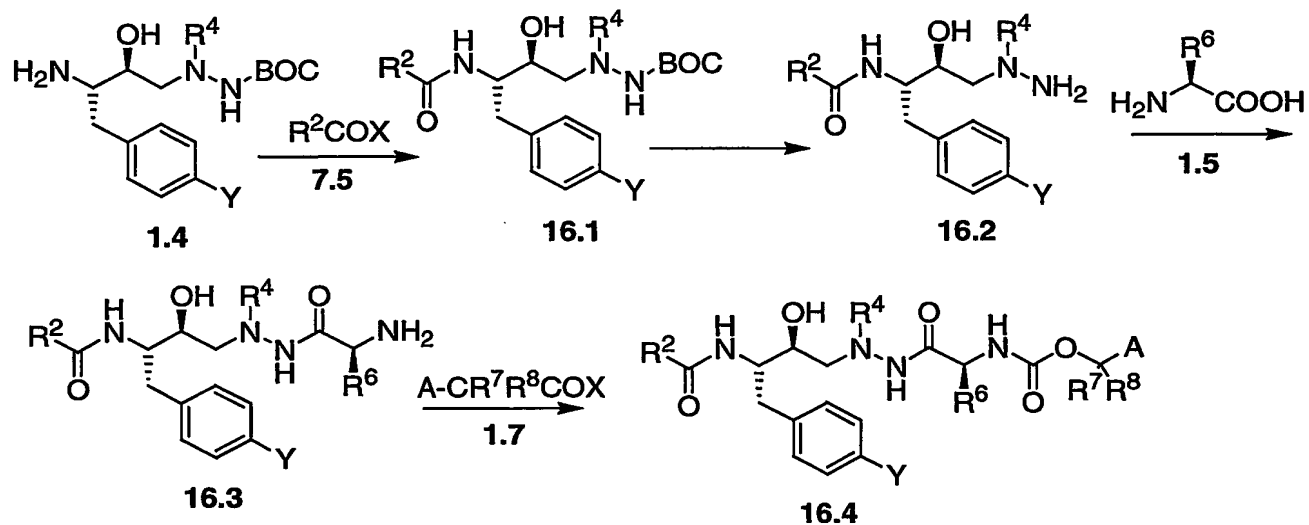
Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

Schemes 19c and 19d illustrate the preparation of the phosphonate esters 5 in which X is sulfur. As shown in Scheme 19c, the amine 5.9 is reacted, as described above, with the quinoline carboxylic acid derivative 19a.1 to yield the amide product 19c.1. The BOC protecting group is then removed, as described above, to give the amine 19c.2. The latter compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19c.3.

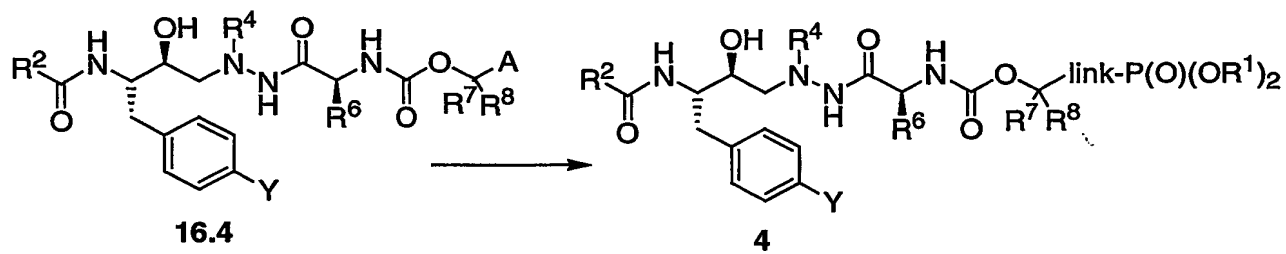
The procedures illustrated in Scheme 19c depict the preparation of the phosphonate esters 19c.3 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19d illustrates the conversion of compounds 19c.3 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are

illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents **19a.1** is described below, (Schemes 53 - 56).

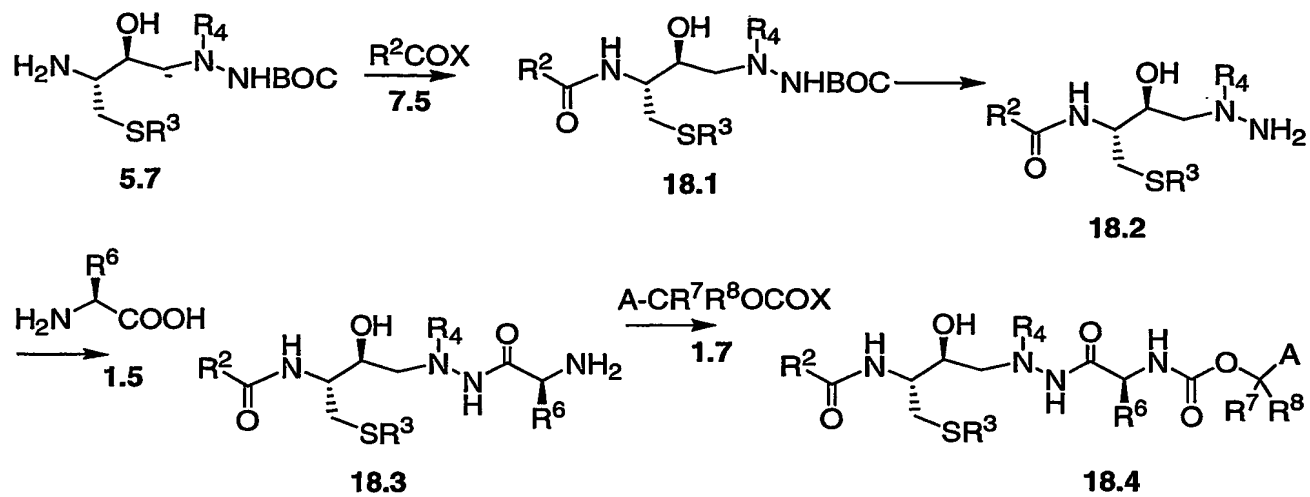
Scheme 16



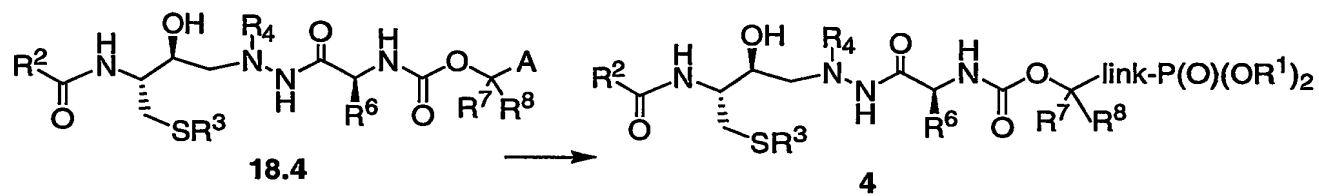
Scheme 17



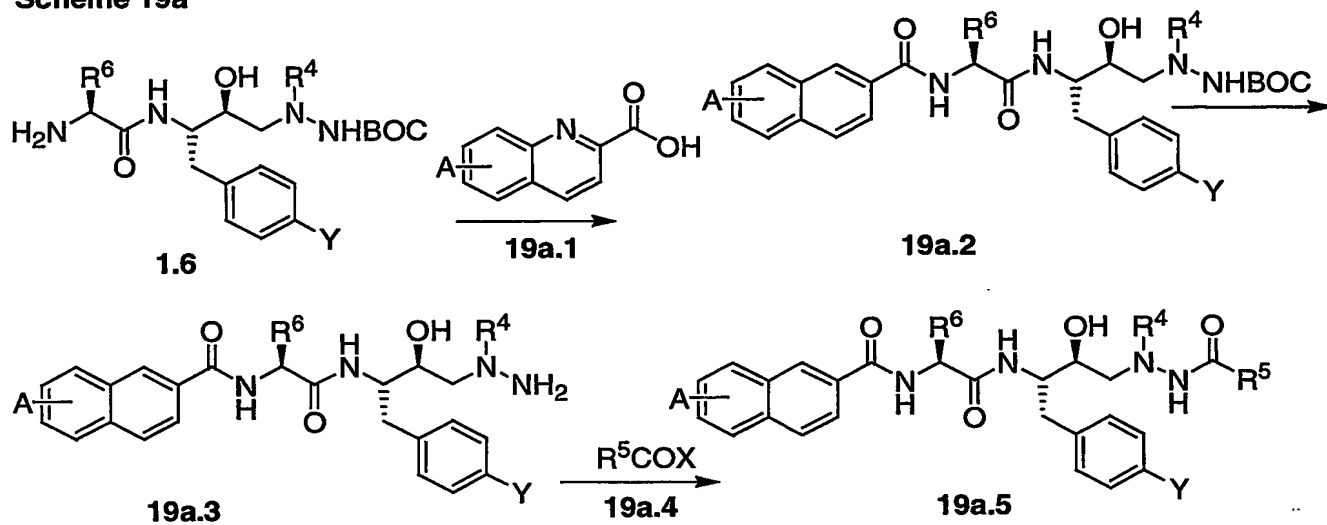
Scheme 18



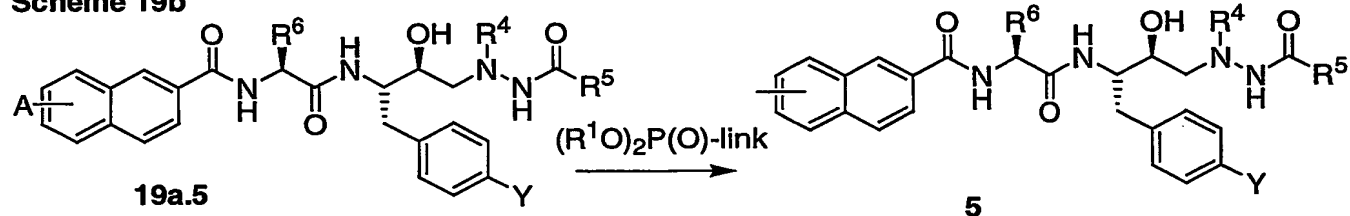
Scheme 19



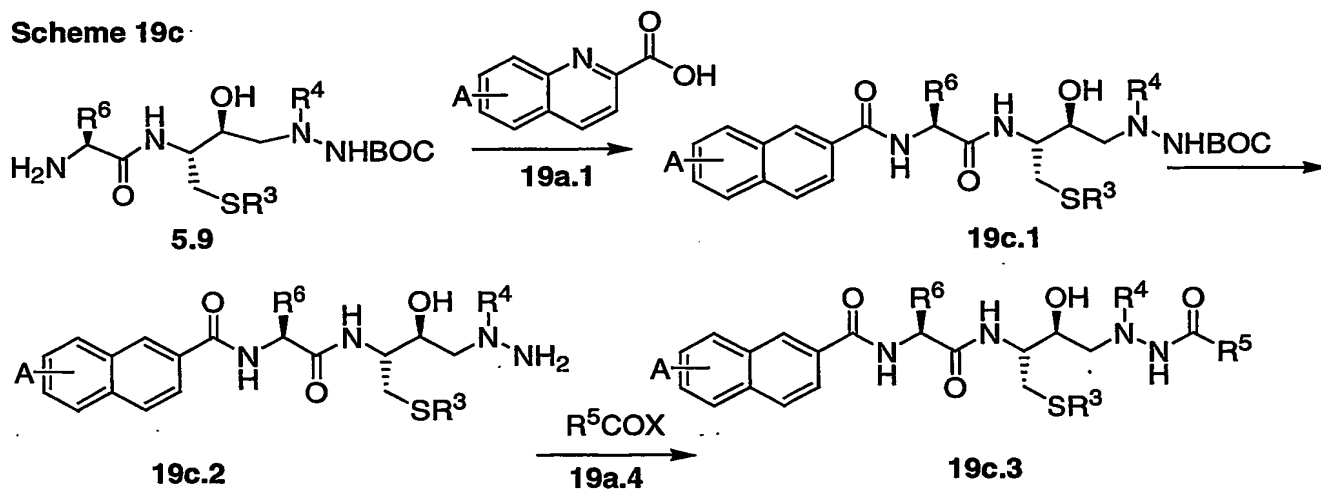
Scheme 19a



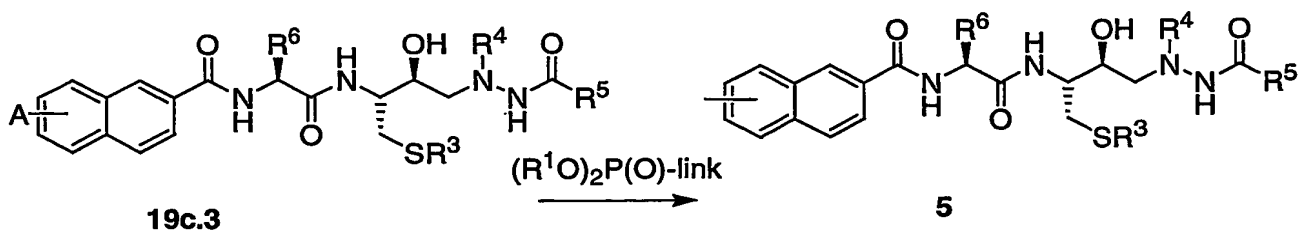
Scheme 19b



Scheme 19c



Scheme 19d



Preparation of carbamates.

The phosphonate esters **1** and **4**, and the phosphonate ester **1-7** in which the R^2CO or R^5CO groups are formally derived from the carboxylic acids **C38 - C49** (Chart 2c) contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 20 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 20, in the general reaction generating carbamates, a carbinol **20.1**, is converted into the activated derivative **20.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **20.2** is then reacted with an amine **20.3**, to afford the carbamate product **20.4**. Examples 1 – 7 in Scheme 20 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 20, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **20.5**. In this procedure, the carbinol **20.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **20.6**. The latter compound is then reacted with the amine component **20.3**, in the presence of an organic or inorganic base, to afford the carbamate **20.7**. For example, the chloroformyl compound **20.6** is reacted with the amine **20.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **20.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 20, Example 2 depicts the reaction of the chloroformate compound **20.6** with imidazole to produce the imidazolide **20.8**. The imidazolide product is then reacted with the amine **20.3** to yield the carbamate **20.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is

conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 20 Example 3, depicts the reaction of the chloroformate 20.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 20.10. The reaction is

5 conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 20.19 - 20.24 shown in Scheme 20, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 20.19, N-hydroxysuccinimide 20.20, or pentachlorophenol, 20.21, the mixed carbonate 20.10 is obtained by the reaction of the
10 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 20.22 or 2-hydroxypyridine 20.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

15 Scheme 20 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 20.8 is employed. In this procedure, a carbinol 20.5 is reacted with an equimolar amount of carbonyl diimidazole 20.11 to prepare the intermediate 20.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 20.8 is then reacted with an equimolar amount of the
20 amine R'NH₂ to afford the carbamate 20.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 20.7.

Scheme 20, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole 20.13. In this procedure, a carbinol ROH is reacted at ambient
25 temperature with an equimolar amount of benztriazole carbonyl chloride 20.12, to afford the alkoxycarbonyl product 20.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine R'NH₂ to afford the carbamate 20.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
30 to about 80° as described in Syn., 1977, 704.

Scheme 20, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 20.14, is reacted with a carbinol 20.5 to afford the intermediate alkyloxycarbonyl

intermediate **20.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **20.7**. The procedure in which the reagent **20.15** is derived from hydroxybenztriazole **20.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **20.15** is derived from N-hydroxysuccinimide **20.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **20.15** is derived from 2-hydroxypyridine **20.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **20.15** is derived from 4-nitrophenol **20.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **20.14** is conducted in an inert organic solvent at ambient temperature.

Scheme 20, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides **20.16**. In this procedure, an alkyl chloroformate **20.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **20.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **20.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

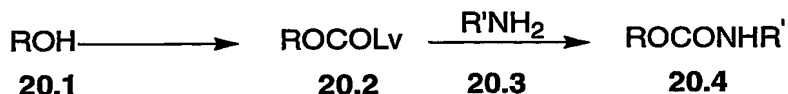
Scheme 20, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **20.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **20.7**.

Scheme 20, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **20.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **20.7**.

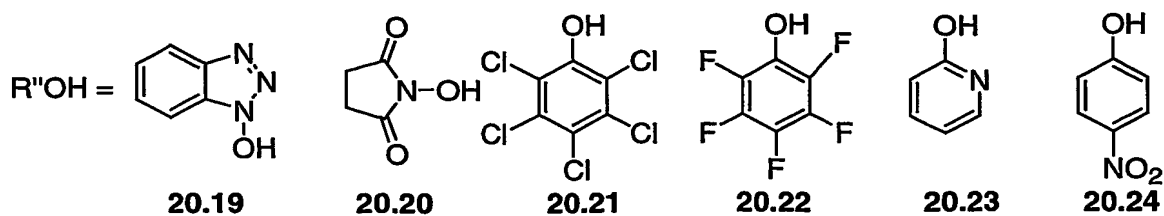
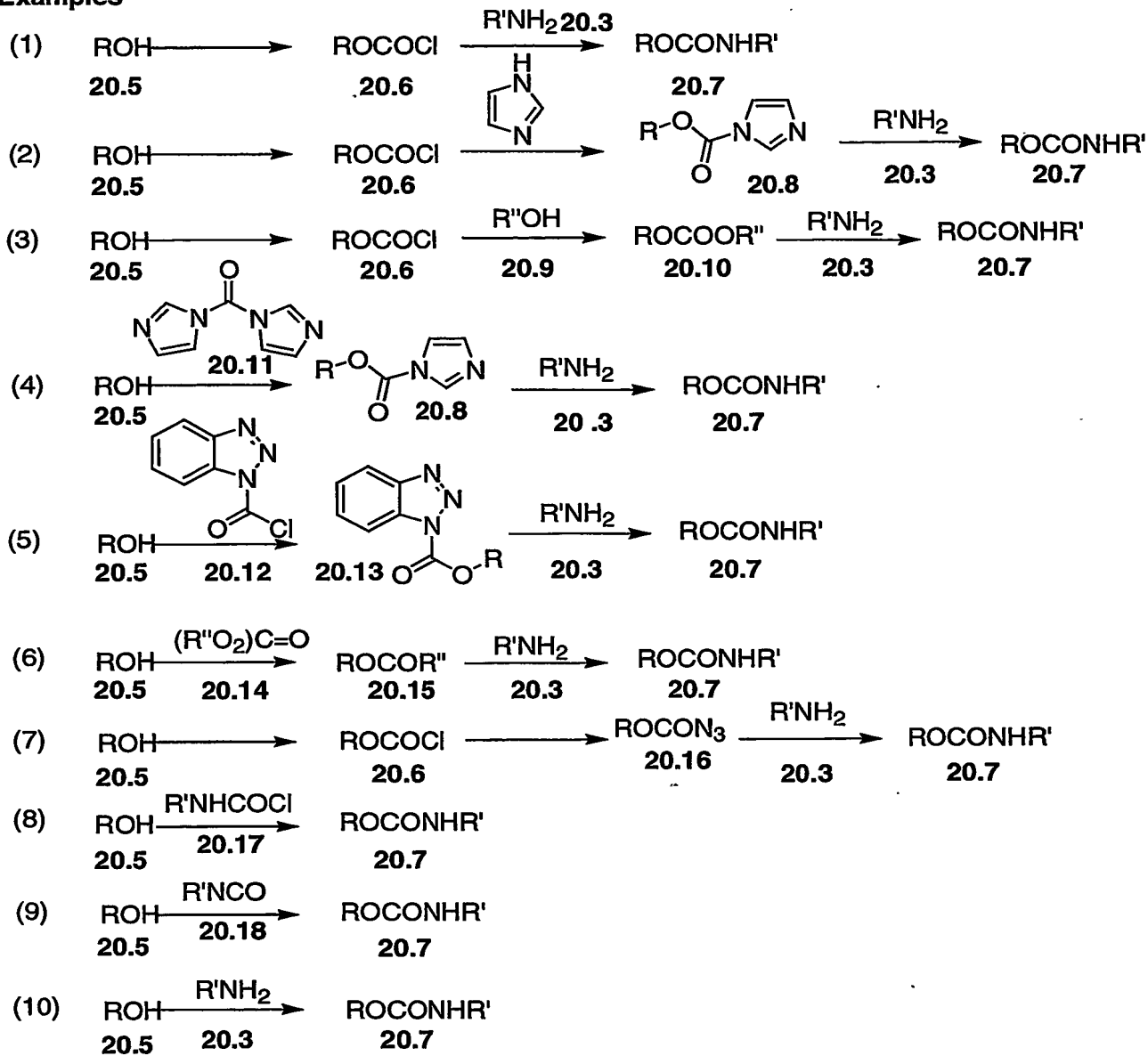
Scheme 20, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **20.7**.

Scheme 20

General reaction



Examples



Preparation of the reagents A-CR⁷R⁸OCOX.

The reagents A-CR⁷R⁸OCOX **1.7** are prepared from the corresponding carbinols A-CR⁷R⁸OH, using procedures such as those described above in Scheme 20. Examples of the preparation of the carbinols A-CR⁷R⁸OH and the derived reagents **1.7** are shown below in Schemes 21-26. The activation methods for the conversion of the carbinols A-CR⁷R⁸OH to the reagents A-CR⁷R⁸OCOX are interchangeable between the different alcohols A-CR⁷R⁸OH.

Scheme 21 depicts the preparation of phosphonate-containing reagents **21.2** in which the phosphonate is linked by means of an alkylene chain. In this procedure, a dialkyl hydroxyalkyl phosphonate **21.1** is reacted with phosgene, or an equivalent reagent, to afford the chloroformate **21.2**, as described above in Scheme 20, Example 1. The reaction is conducted in an inert organic solvent such as dichloromethane or toluene, at from about 0° to ambient temperature.

For example, as shown in Scheme 21, Example 1, a dialkyl hydroxymethylphosphonate **21.3** (Aldrich) is reacted with excess phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 197, 1965, to afford the chloroformyl product **21.4**.

Scheme 21, Example 2 illustrates the analogous conversion of a dialkyl hydroxyethyl phosphonate **21.5** (Aldrich) into the chloroformate derivative **21.6**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Scheme 21, Example 3 illustrates the analogous conversion of a dialkyl phosphono-substituted tert. butanol **21.7**, prepared as described in Fr.2462440, into the chloroformate derivative **21.8**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Using the above procedures, but employing, in place of the phosphonates **21.3**, **21.5** or **21.7**, different dialkyl hydroxyalkyl phosphonates **21.1**, the corresponding products **21.2** are obtained.

Scheme 22 depicts the preparation of phosphonate-containing reagents **22.2** in which the phosphonate is linked by means of a phenyl ring. In this procedure, a dialkyl

hydroxyalkylphenyl phosphonate **22.1** is converted, as described above, into an activated chloroformyl derivative **22.2**, using the procedures described above in Scheme 20.

For example, a dialkyl 4-hydroxymethylphenylphosphonate **22.3** (Aldrich) is reacted in tetrahydrofuran with an equimolar amount of the 2-pyridyl carbonate **22.4**, prepared as

5 described in Tet. Let., 1991, 4251, to afford the product **22.5**.

Using the above procedure, but employing, in place of a dialkyl hydroxyphenylphosphonate **22.3**, different dialkyl hydroxyphenyl phosphonates **22.1**, the corresponding products **22.2** are obtained.

10 Scheme 23 depicts the preparation of phosphonate containing reagents **23.4** in which the phosphonate group is linked by means of an alkylene chain incorporating a heteroatom O, S or N. In this procedure, a dialkyl hydroxy-, thio- or alkylaminoalkylphosphonate **23.1** is alkylated by reaction with a bromoalkanol **23.2**. The alkylation reaction is conducted at from ambient temperature to about 70° in a polar organic solvent such as dimethylformamide,

15 dioxan or acetonitrile, in the presence of a base. In cases in which X is oxygen, a strong base such as lithium hexamethyldisilylazide or potassium tert-butoxide is employed. In cases in which X is sulfur or alkylamino, an inorganic base such as potassium carbonate or cesium carbonate is used. The product **23.3** is then converted into an activated derivative **23.4** by means of one of the methods described above in Scheme 20.

20 For example, as shown in Scheme 23, Example 1, a dialkyl 2-mercaptoethylphosphonate **23.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, is reacted with one molar equivalent of bromoethanol **23.6**, in dimethylformamide at 60° in the presence of cesium carbonate, to afford the thioether product **23.7**. This compound is then reacted with pentafluorophenyl carbonate **23.8**, (Fluorochem) in dimethylformamide solution at ambient

25 temperature in the presence of triethylamine, to afford the pentafluorophenoxycarbonyl product **23.9**.

As a further example of the method of Scheme 23, as shown in Example 2, a dialkyl methylaminomethyl phosphonate **23.10**, (AsInEx Inc.) is reacted in dimethylformamide at 70° with one molar equivalent of 5-bromo-2-hydroxy-2-methylpentane **23.11**, prepared as

30 described in J. Med. Chem., 1994, 37, 2343, and potassium carbonate, to afford the amine product **23.12**. The product is then converted, as described above, into the pentafluorophenyl formate derivative **23.13**.

Using the above procedures, but employing, in place of a dialkyl 2-mercaptoethylphosphonate **23.5**, or a dialkyl methylaminomethyl phosphonate **23.10**, different hydroxy, mercapto or aminoalkylphosphonates **23.1**, and/or different bromoalkanols **23.2**, and/or different activation methods, the corresponding products **23.4** are obtained.

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Scheme **24** illustrates the preparation of phosphonate containing reagents **24.4** in which the phosphonate group is linked by means of an alkylene chain incorporating an N-alkyl group. In this procedure, a dialkyl formylalkyl phosphonate **24.1** is reacted with an alkylaminoalkanol **24.2** under reductive amination conditions, so as to afford the product **24.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this reaction, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reduction reaction can also be performed by hydrogenation in the presence of a palladium catalyst and hydrogen or a hydrogen donor. The reaction product **24.3** is then transformed into the activated derivative **24.4** by means of one of the procedures described above in Scheme **20**.

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As shown in Scheme **24**, Example **1**, a dialkyl formylmethylphosphonate **24.5** (Aurora) is reacted with methylaminoethanol **24.6**, in the presence of sodium cyanoborohydride, to afford the coupled product **24.7**. This compound is then reacted with an equimolar amount of chlorocarbonylbenztriazole **20.13**, in toluene at 80°, in the presence of one molar equivalent of triethylamine, as described in Syn., 1977, 704, to yield the product **24.8**.

As a further example of the method of Scheme **24**, as shown in Example **2**, the aldehyde **24.5** is reacted with 2-hydroxy-2-methyl-3-methylaminopropane **24.10**, under reductive amination conditions, to afford the amine product **24.11**. The latter compound is then reacted with phosgene, or an equivalent thereof, as described above, to afford the chloroformyl product **24.12**.

Using the above procedures, but employing, in place of the phosphonates **24.5**, different phosphonates **24.1**, and/or in place of the aminoalkanols **24.6** or **24.10**, different

aminoalkylalkanols **24.2**, and/or different activation methods described in Scheme **20**, the corresponding products **24.4** are obtained.

Scheme **25** illustrates the preparation of phosphonate containing reagents **25.2** in which the phosphonate group is linked by means of an alkylene chain incorporating an acetylenic linkage. In this procedure, a dialkyl hydroxyalkynyl phosphonate **25.1** is converted, by means of one of the procedures described in Scheme **20**, into the activated formyl derivative **25.2**.

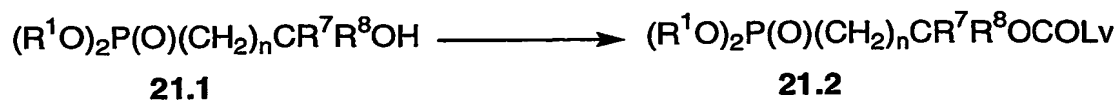
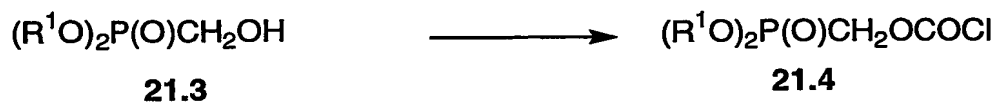
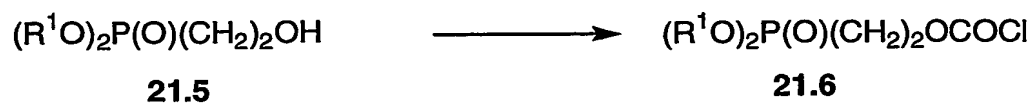
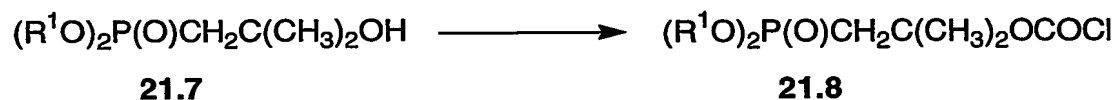
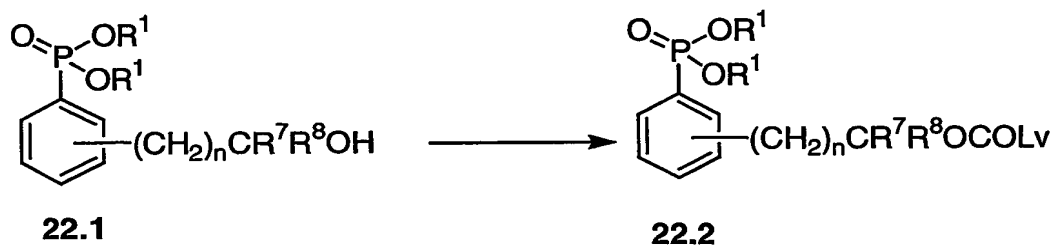
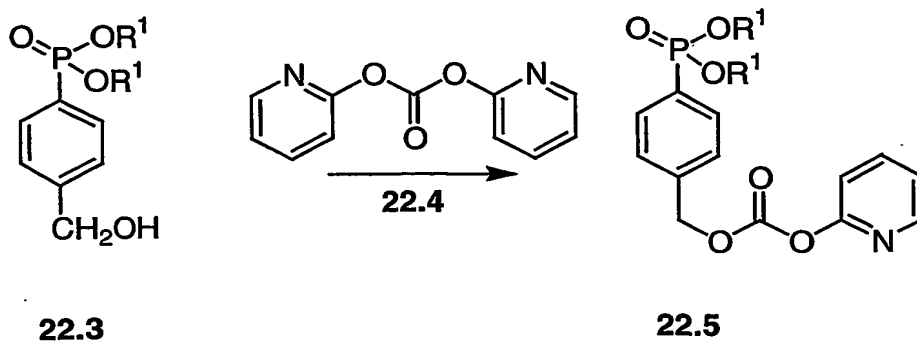
For example, a dialkyl hydroxypropynyl phosphonate **25.3** prepared as described in J. Org. Chem., 1987, 52, 4810, is reacted with one molar equivalent of di(succinimidyloxy)carbonate **25.4**, prepared as described in Tet. Lett, 1992, 2781, in dichloromethane at ambient temperature, to afford the product **25.5**.

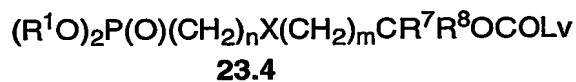
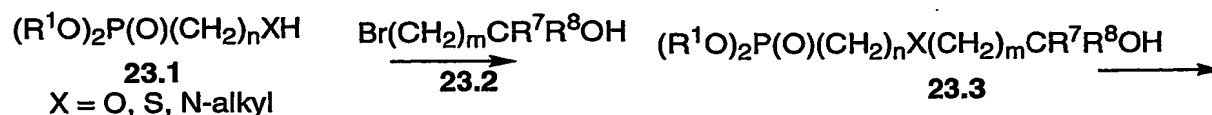
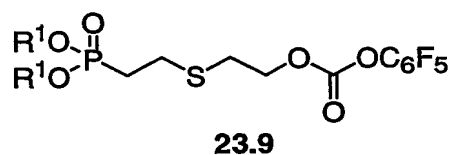
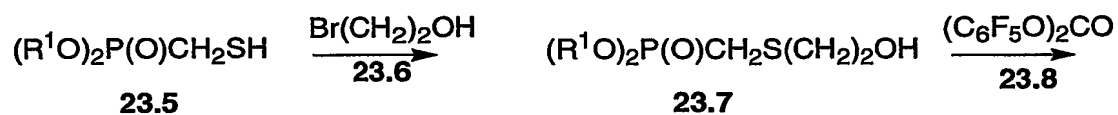
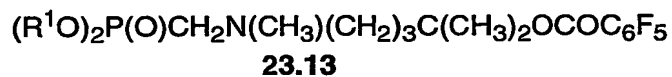
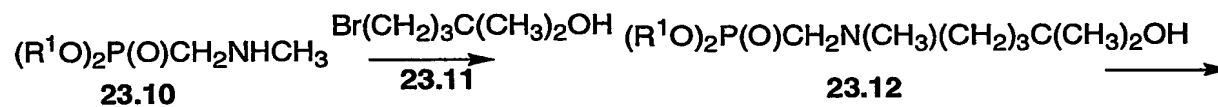
Using the above procedures, but employing, in place of the dialkyl hydroxypropynyl phosphonate **25.3**, different dialkyl hydroxyalkynyl phosphonates **25.1**, the corresponding products **25.2** are obtained.

Scheme **26** illustrates the preparation of phosphonate containing reagents **26.2** in which the phosphonate group is linked by means of an alkylene chain incorporating an olefinic linkage. In this procedure, a dialkyl hydroxyalkenyl phosphonate **26.1** is converted, by means of one of the procedures described in Scheme **20**, into the activated formyl derivative **26.2**.

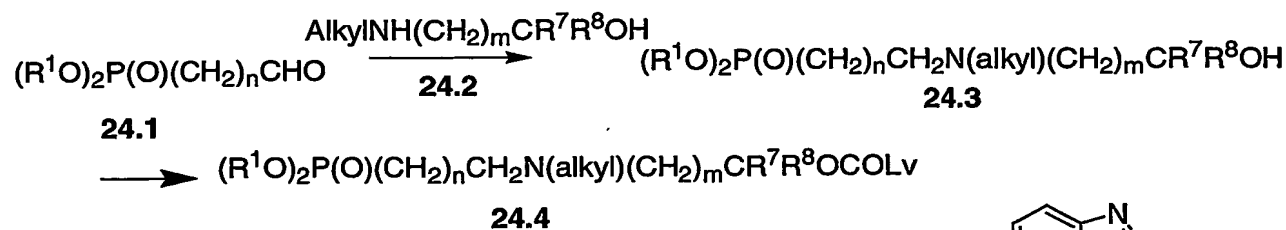
For example, a dialkyl propenylphosphonate **26.3**, prepared as described in Zh. Obschei. Khim., 1974, 44, 18343, is reacted with phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to afford the chloroformyl product **26.4**.

Using the above procedures, but employing, in place of the dialkyl hydroxypropenyl phosphonate **26.3**, different dialkyl hydroxyalkenyl phosphonates **26.1**, the corresponding products **26.2** are obtained.

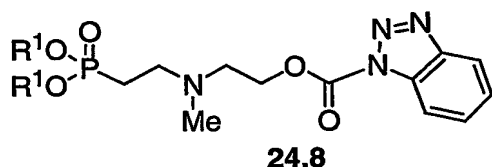
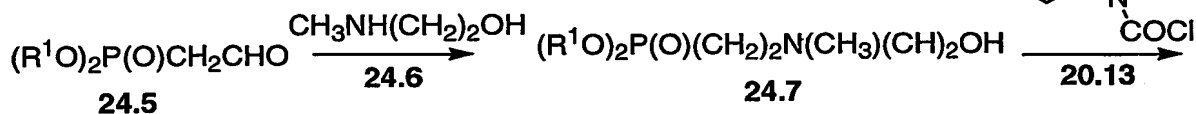
Scheme 21**Method****Example 1****Example 2****Example 3****Scheme 22****Method****Example**

Scheme 23**Method****Example 1****Example 2**

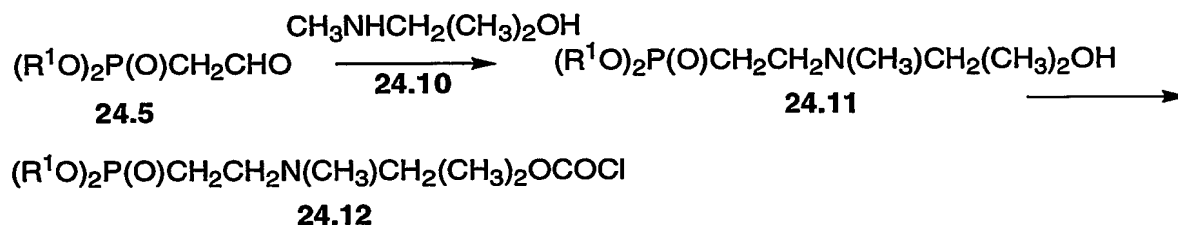
Scheme 24
Method



Example 1

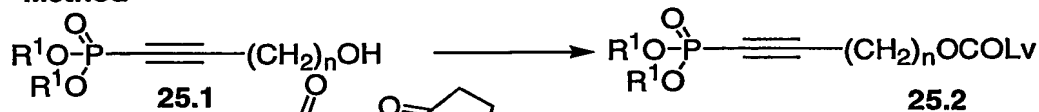


Example 2

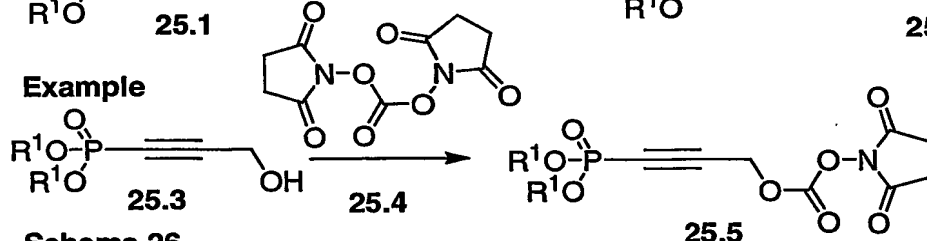


Scheme 25

Method

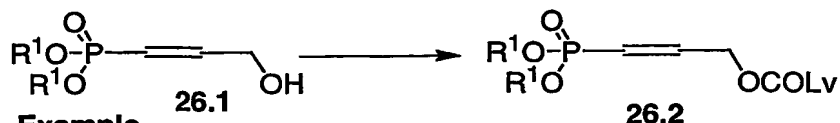


Example



Scheme 26

Method



Example



Preparation of the oxirane reactants 7.1.

- 5 The oxirane reactants 7.1 are obtained by means of chemical transformations applied to variously substituted phenylalanine derivatives. In the methods described below, the phosphonate moiety can be introduced into the molecule at any appropriate stage in the synthetic sequence, or after the intermediates are incorporated into the phosphonate esters 2.
- 10 Scheme 27 depicts the preparation of oxirane reactants 27.5 in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 27.1 is converted into the cbz-protected derivative, using the procedures described above in Scheme 3. The protected product 27.2 is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane 27.3. The latter compound is then reacted with a dialkyl
- 15 phosphite 27.4, in the presence of a palladium catalyst, to afford the phosphonate ester 27.5. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.
- For example, 4-bromophenylalanine 27.6, prepared as described in Biotech. Lett., 1994, 16, 373, is converted, as described above, (Scheme 3), into the oxirane 27.7. This compound is
- 20 then reacted, in toluene solution at reflux, with a dialkyl phosphite 27.4, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 27.8.
- Using the above procedures, but employing, in place of 4-bromophenylalanine 27.6, different bromo-substituted phenylalanines 27.1, and/or different dialkyl phosphites, the corresponding
- 25 products 27.5 are obtained.

Scheme 28 illustrates the preparation of oxiranes 28.4 in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a carbobenzyloxy protected bromo-substituted phenylalanine 27.2, prepared as described above, is coupled, in the presence of a

30 palladium catalyst, with a dialkyl alkenylphosphonate 28.1, to afford the coupled product 28.2. The preparation of aryl alkenyl phosphonates by means of a coupling reaction between aryl bromides and alkenyl phosphonates is described in Syn., 1983, 556. The reaction is performed

in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a palladium (II) catalyst, a tertiary base such as triethylamine and a phosphine such as triphenylphosphine and the like, to afford the aryl alkenyl phosphonate product **28.2**. The latter compound is then reduced, for example by reaction with diimide, as described in
5 Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 262, to afford the saturated product **28.3**. The latter compound is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane **28.4**.

For example, the cbz-protected 3-bromophenylalanine **28.5**, prepared as described in Pept. Res., 1990, 3, 176, is coupled, in acetonitrile solution at 100° in a sealed tube, with a dialkyl
10 vinylphosphonate **28.6**, in the presence of palladium (II)acetate, tri-(o-tolyl)phosphine and triethylamine, as described in Syn., 1983, 556, to afford the coupled product **28.7**. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product **28.8**. This material is then converted, using the procedures shown in Scheme 3, into
15 the oxirane **28.9**.

Using the above procedures, but employing, in place of the 3-bromophenylalanine derivative **28.5**, different bromo compounds **27.2**, and/or different alkenyl phosphonates **28.1**, the corresponding products **28.4** are obtained.

20 Scheme 29 illustrates the preparation of oxiranes **29.9** in which the phosphonate group is linked by means of an alkylene chain and an oxygen or sulfur atom. In this procedure, a substituted phenylalanine **29.1** is converted into the methyl ester **29.2** by means of a conventional acid-catalyzed esterification reaction. The hydroxy or mercapto substituent is then protected to afford the derivative **29.3**. The protection of phenyl hydroxyl and mercapto
25 groups is described respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl, 9-fluorenylmethyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-

methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected compound **29.3** is then transformed into the cbz derivative **29.4**, using the procedure described above (Scheme 3). The O or S-protecting group is then removed to produce the phenol or thiol **29.5**. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978 or by the use of mercuric acetate in trifluoroacetic acid. The resultant phenol or thiophenol **29.5** is then reacted with a dialkyl halo or alkylsulfonyloxyalkyl phosphonate **29.6**, to yield the ether or thioether product **29.7**. The alkylation reaction is performed at from ambient temperature to about 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an organic or inorganic base such as dimethylaminopyridine, triethylamine, potassium carbonate or cesium carbonate. The methyl ester is then hydrolyzed, for example by treatment with lithium hydroxide in aqueous tetrahydrofuran, to afford the carboxylic acid **29.8**. The latter compound is then transformed, by means of the reactions shown in Scheme 3, into the oxirane **29.9**.

For example, as illustrated in Scheme 29, Example 1, 4-mercaptophenylalanine **29.10**, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is reacted with methanol at reflux temperature in the presence of p-toluenesulfonic acid, to yield the methyl ester **29.11**. The thiol substituent is then protected by conversion to the S-adamantyl derivative **29.12**, for example by reaction with adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group in the product **29.12** is then protected by conversion to the cbz derivative **29.13**, using the procedure described in Scheme 3. Removal of the S-protecting group, for example by treatment of the thioether **29.13** with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, then affords the thiophenol **29.14**. The latter compound is then reacted in dimethylformamide solution with a dialkyl bromoalkylphosphonate, for example a dialkyl bromoethylphosphonate **29.15**, (Aldrich) in the presence of a base such as cesium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the thioether **29.16**. The methyl

ester is then hydrolyzed as described above, and the resultant carboxylic acid **29.17** is transformed, by means of the reactions shown in Scheme 3, into the oxirane **29.18**.

As a further example of the method of Scheme 29, as shown in Example 2, 3-

hydroxyphenylalanine **29.19** (Fluka) is converted into the methyl ester **29.20**, and the phenolic

5 hydroxyl group is then protected by reaction with one molar equivalent of tert-

butylchlorodimethylsilane and imidazole in dimethylformamide, as described in J. Amer. Chem.

Soc., 94, 6190, 1972, to produce the silyl ether **29.21**. Conversion to the cbz derivative

29.22, as described above, followed by desilylation, using tetrabutylammonium fluoride in

tetrahydrofuran, as described in J. Amer. Chem. Soc., 94, 6190, 1972, then affords the phenol

10 **29.23**. The phenolic hydroxyl group is then reacted in dimethylformamide solution with a

dialkyl trifluoromethanesulfonyloxymethyl phosphonate, **29.24**, prepared as described in Tet.

Lett., 1986, 27, 1477, and a base such as triethylamine, to afford the ether **29.25**. The methyl

ester is then hydrolyzed, as described above, and the resultant carboxylic acid **29.26** is then

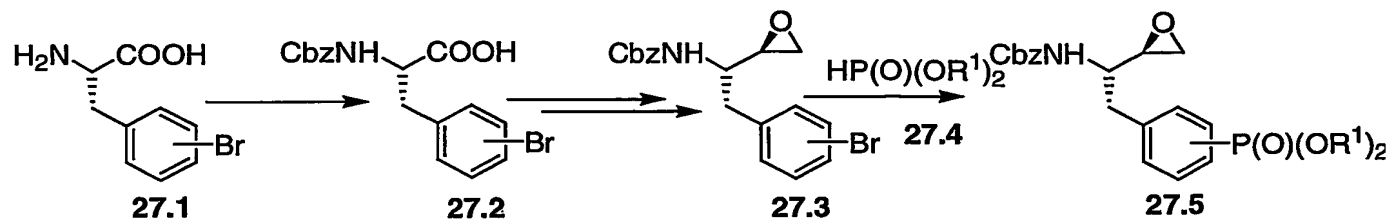
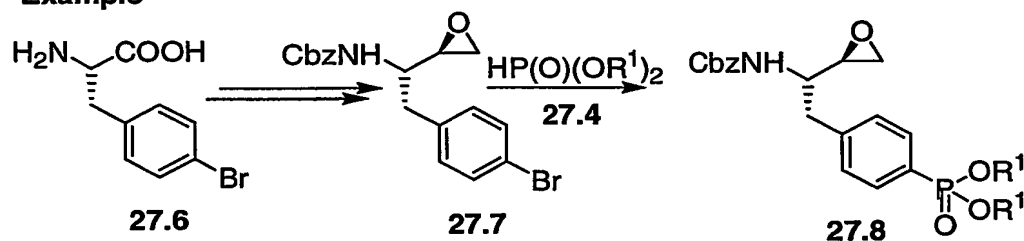
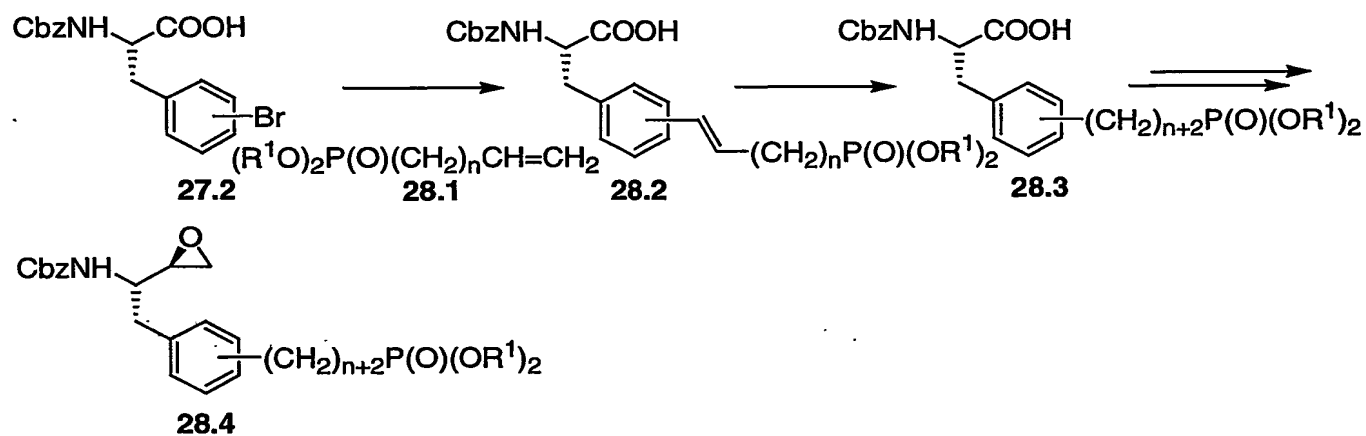
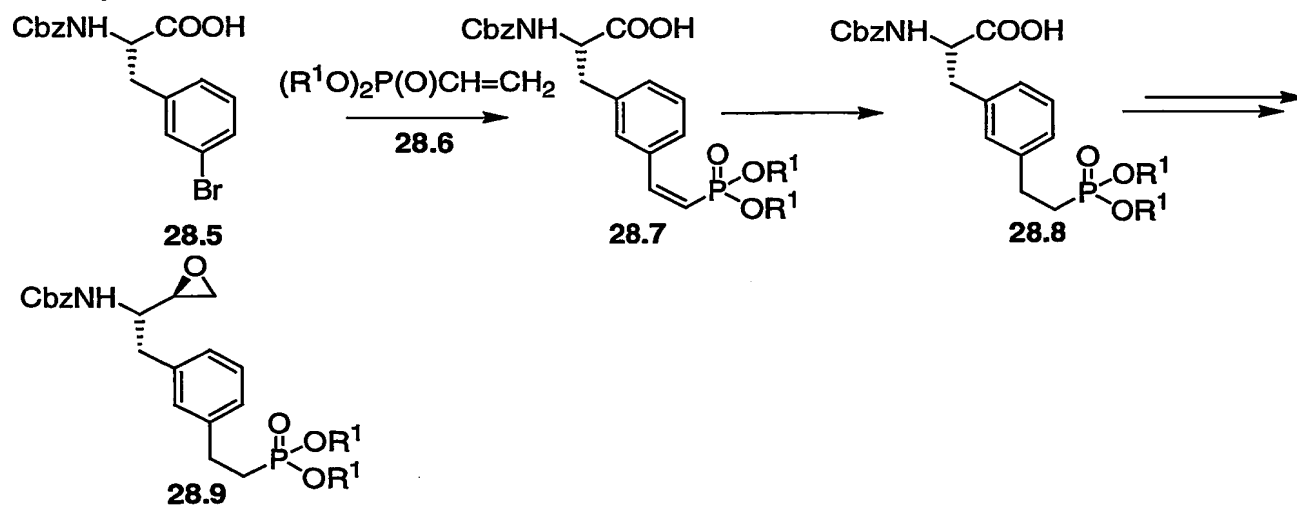
transformed, by means of the series of reactions shown in Scheme 3, into the oxirane **29.27**.

15 Using the above procedures, but employing, in place of the bromoethyl phosphonate **29.15**, or

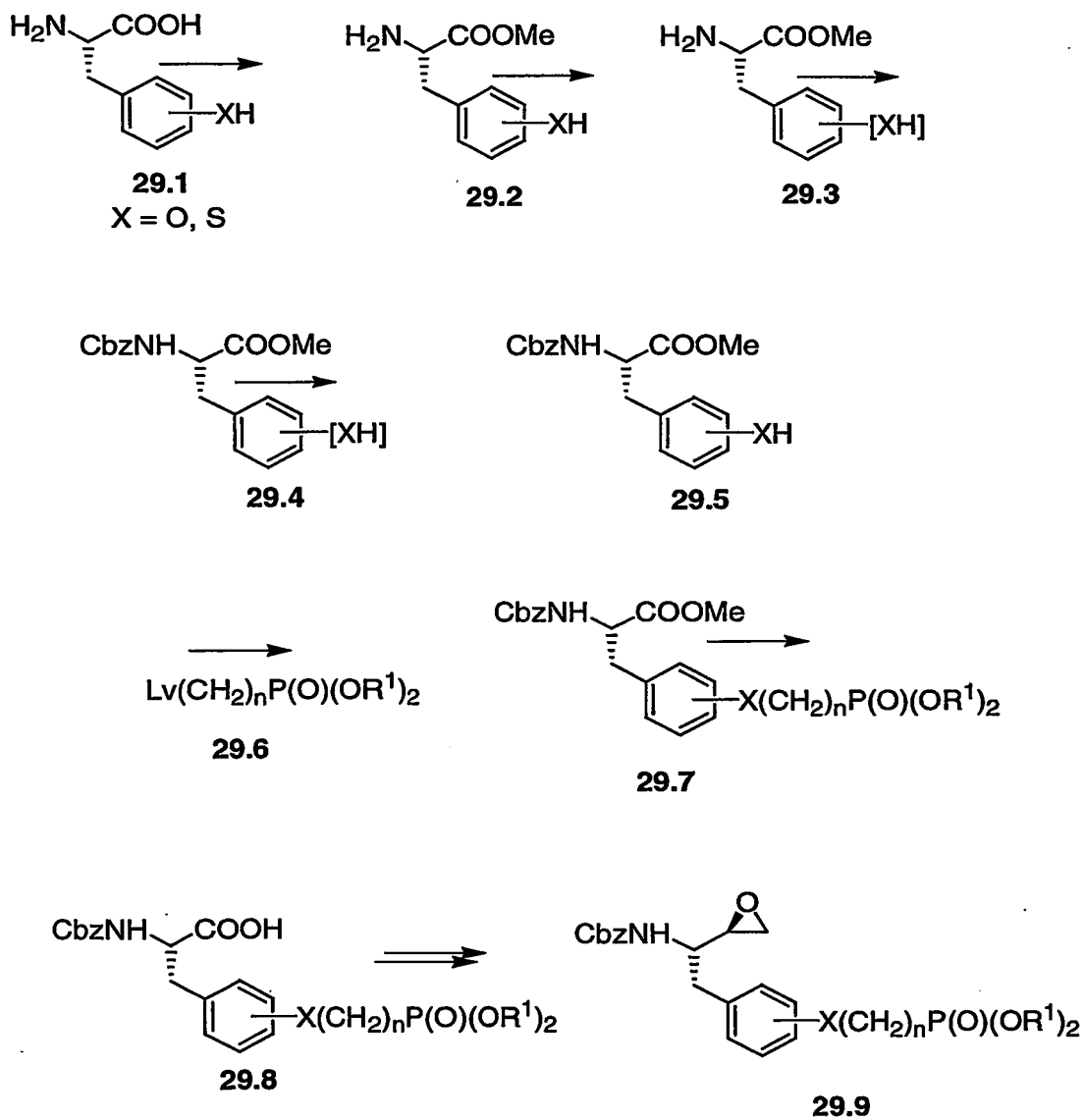
the trifluoromethanesulfonyloxymethyl phosphonate **29.24**, different bromoalkyl or

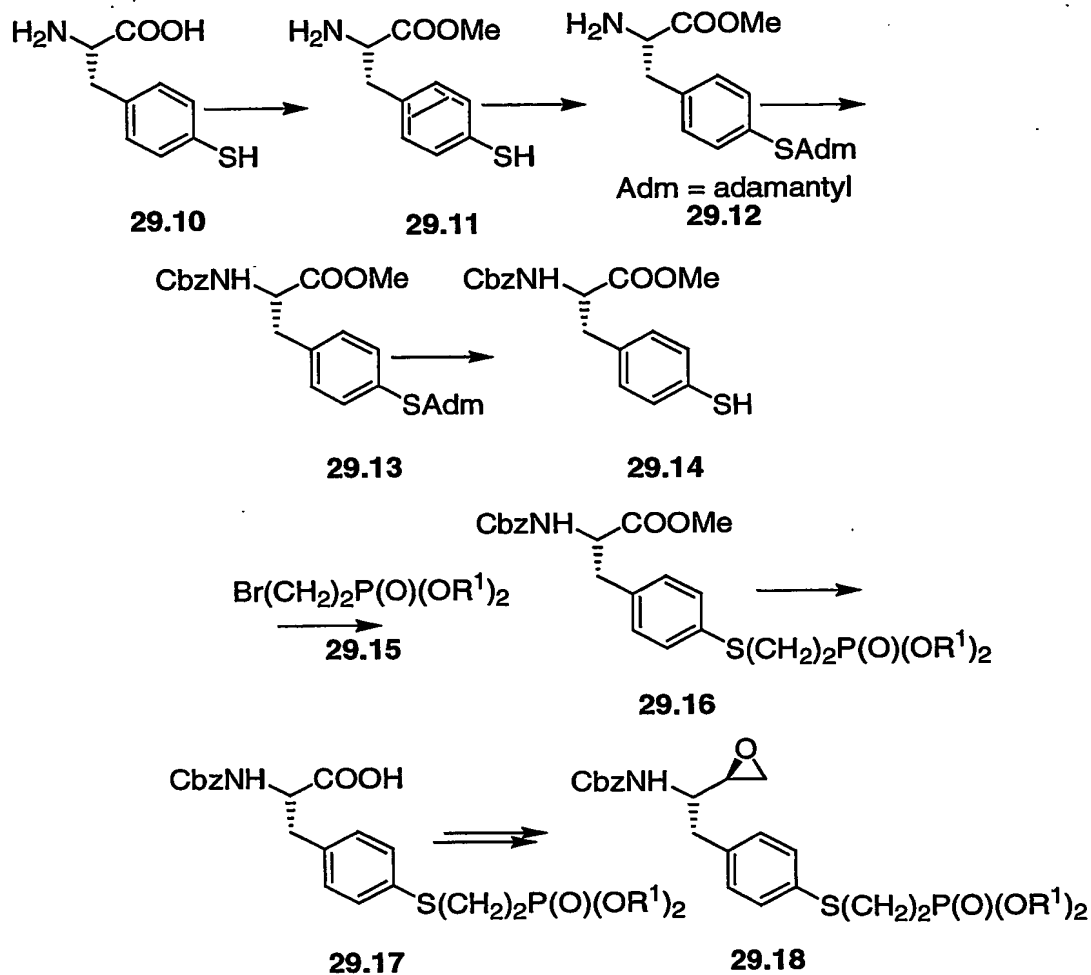
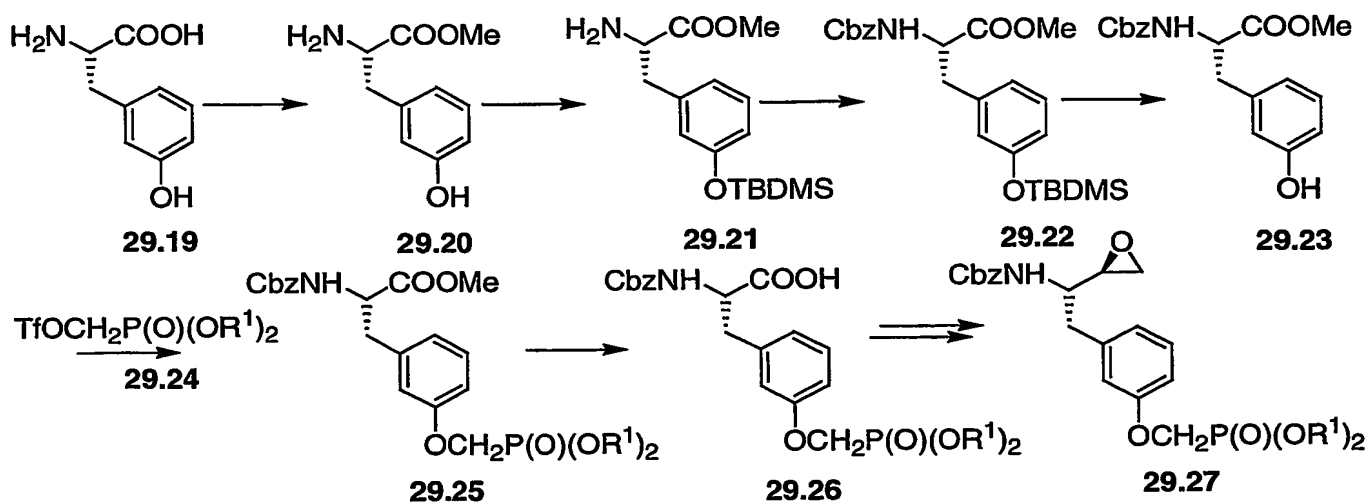
trifluoromethanesulfonyloxyalkyl phosphonates **29.6**, and/or different phenylalanine derivatives

29.1, the corresponding products **29.9** are obtained.

Scheme 27**Method****Example****Scheme 28****Method****Example**

Scheme 29



Example 1**Example 2**

Preparation of the phosphonate-containing thiophenol derivatives 10.1.

Schemes 30 - 39 describe the preparation of phosphonate-containing thiophenol derivatives 10.1 which are employed as described above (Schemes 10 and 11) in the preparation of the phosphonate ester intermediates 2.

Scheme 30 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 30.1 is protected, as described above (Scheme 29) to afford the protected product 30.2. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 30.3. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described above, (Scheme 29). The thiol protecting group is then removed, as described above, to afford the thiol 30.4.

For example, 3-bromothiophenol 30.5 is converted into the 9-fluorenylmethyl (Fm) derivative 30.6 by reaction with 9-fluorenylmethyl chloride and diisopropylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 30.3, as described for the preparation of the phosphonate 27.8 (Scheme 27), to afford the phosphonate ester 30.7. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 30.8.

Using the above procedures, but employing, in place of 3-bromothiophenol 30.5, different thiophenols 30.1, and/or different dialkyl phosphites 30.3, the corresponding products 30.4 are obtained.

Scheme 31 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 31.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 31.3. The latter compound is reacted with a halodialkyl phosphite 31.4 to afford the product 31.5; deprotection then affords the thiophenol 31.6.

For example, 4-bromothiophenol 31.7 is converted into the S-triphenylmethyl (trityl) derivative 31.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **31.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodialkyl phosphite **31.10** to afford the phosphonate **31.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **31.12**.
Using the above procedures, but employing, in place of the bromo compound **31.7**, different halo compounds **31.2**, and/or different halo dialkyl phosphites **31.4**, there are obtained the corresponding thiols **31.6**.

Scheme 32 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **32.1**. This compound is reacted with a sodium dialkyl phosphite **32.2** or a trialkyl phosphite, to give the displacement or rearrangement product **32.3**, which upon deprotection affords the thiophenol **32.4**.

For example, 2-methylthiophenol **32.5** is protected by conversion to the benzoyl derivative **32.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **32.7**. This material is reacted with a sodium dialkyl phosphite **32.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **32.8**. Alternatively, the bromomethyl compound **32.7** can be converted into the phosphonate **32.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **32.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **32.8**. Deprotection of the phosphonate **32.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **32.9**.

Using the above procedures, but employing, in place of the bromomethyl compound **32.7**, different bromomethyl compounds **32.1**, there are obtained the corresponding thiols **32.4**.

Scheme 33 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **33.1** is reacted with a dialkyl hydroxyalkylphosphonate **33.2** under

the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product 33.3. Deprotection then yields the O- or S-linked products 33.4.

For example, the substrate 3-hydroxythiophenol, 33.5, is converted into the monotrityl ether 33.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 33.7 in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound 33.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 33.9.

Using the above procedures, but employing, in place of the phenol 33.5, different phenols or thiophenols 33.1, and different dialkylphosphonates 33.2 there are obtained the corresponding thiols 33.4.

Scheme 34 illustrates the preparation of thiophenols 34.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 34.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 34.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 34.3. Deprotection then affords the thiol 34.4.

For example, 4-methylaminothiophenol 34.5 is reacted with one equivalent of acetyl chloride, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 34.6. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate 34.7, the preparation of which is described in *Tet. Lett.*, 1986, 27, 1477, to afford the displacement product 34.8. Preferably, equimolar amounts of the phosphonate 34.7 and the amine 34.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 34.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in *J. Amer. Chem. Soc.*, 85, 1337, 1963, then affords the thiophenol 34.9.

Using the above procedures, but employing, in place of the thioamine 34.5, different phenols, thiophenols or amines 34.1, and/or different phosphonates 34.2, there are obtained the corresponding products 34.4.

Scheme 35 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 35.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 35.1 is reacted with a dialkyl bromoalkyl phosphonate 35.2 to afford the product 35.3. Deprotection then affords the free thiophenol 35.4.

For example, 3-hydroxythiophenol 35.5 is converted into the S-trityl compound 35.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 35.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 35.8. Deprotection, as described above, then affords the thiol 35.9.

Using the above procedures, but employing, in place of the phenol 35.5, different phenols, thiophenols or amines 35.1, and/or different phosphonates 35.2, there are obtained the corresponding products 35.4.

Scheme 36 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 36.2 is coupled with an aromatic bromo compound 36.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 36.4, or the saturated analog 36.6.

For example, 3-bromothiophenol is converted into the S-Fm derivative 36.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 36.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a

palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **36.9**. Deprotection, as described above, then affords the thiol **36.10**. Optionally, the initially formed unsaturated phosphonate **36.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **36.11**, which upon deprotection affords the thiol **36.12**.

Using the above procedures, but employing, in place of the bromo compound **36.7**, different bromo compounds **36.1**, and/or different phosphonates **36.2**, there are obtained the corresponding products **36.4** and **36.6**

Scheme **37** illustrates the preparation of an aryl-linked phosphonate ester **37.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **37.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **37.3** which is deprotected to yield the thiol **37.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **37.5**. This material is reacted with diethyl 4-bromophenylphosphonate **37.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **37.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **37.8**.

Using the above procedures, but employing, in place of the boronate **37.5**, different boronates **37.1**, and/or different phosphonates **37.2**, there are obtained the corresponding products **37.4**.

Scheme **38** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol

38.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 38.2, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 38.3 is then deprotected to afford the thiol 38.4. For example, 1,4-

5 dimercaptobenzene is converted into the monobenzoyl ester 38.5 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 38.5 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 38.6, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 38.7 thus obtained is deprotected, as described above, to afford the thiol 38.8.

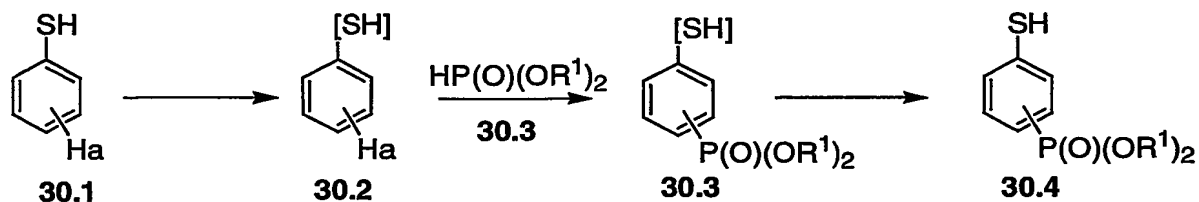
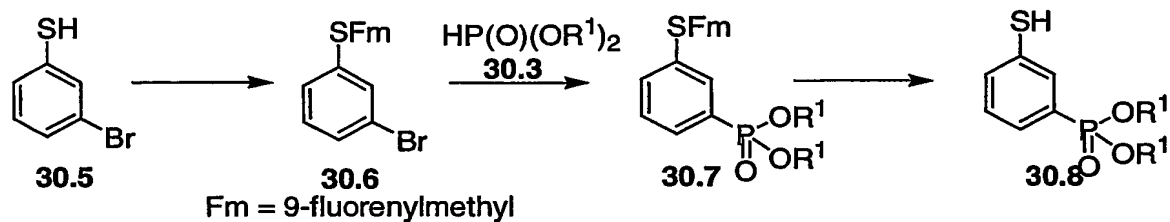
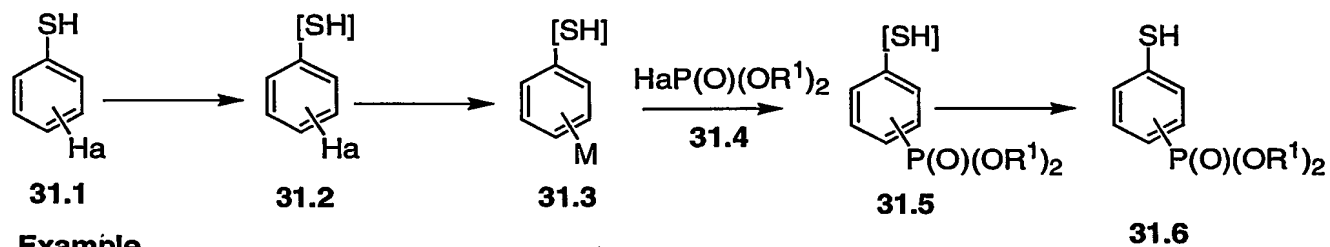
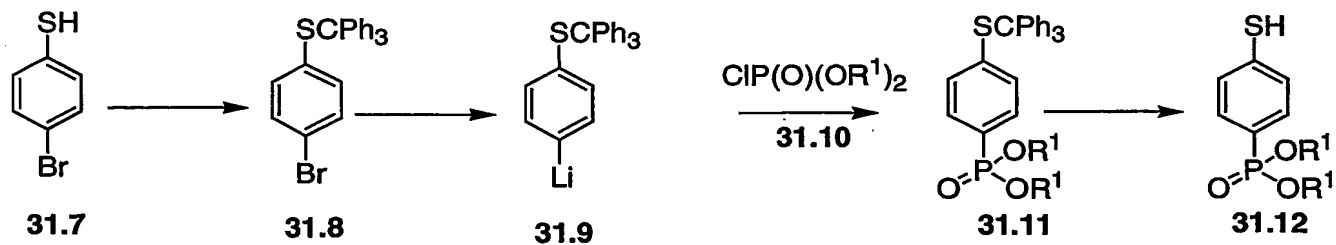
Using the above procedures, but employing, in place of the thiophenol 38.5, different phenols, thiophenols or amines 38.1, and/or different phosphonates 38.2, there are obtained the corresponding products 38.4.

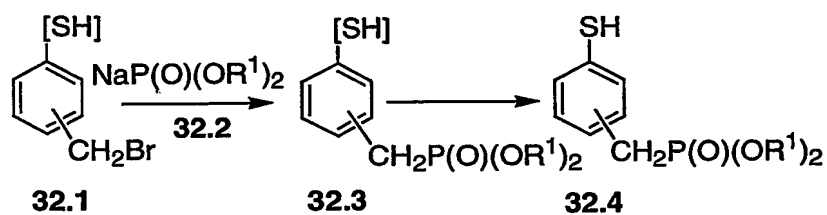
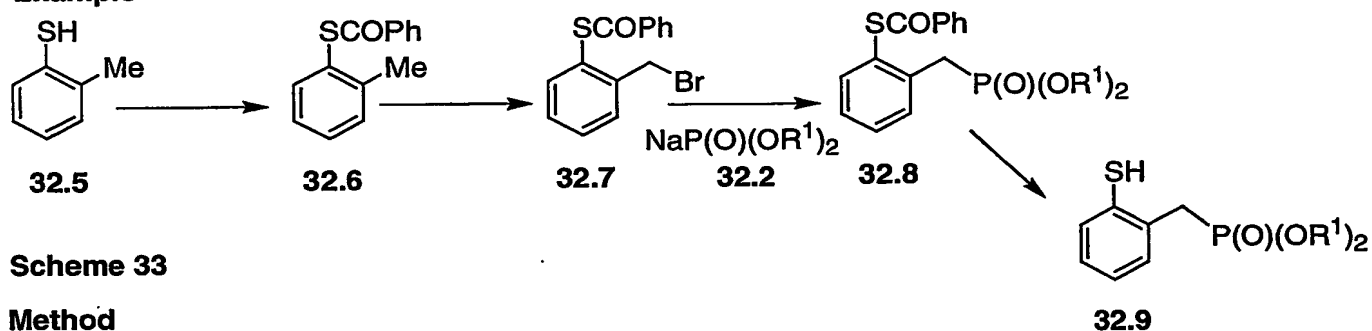
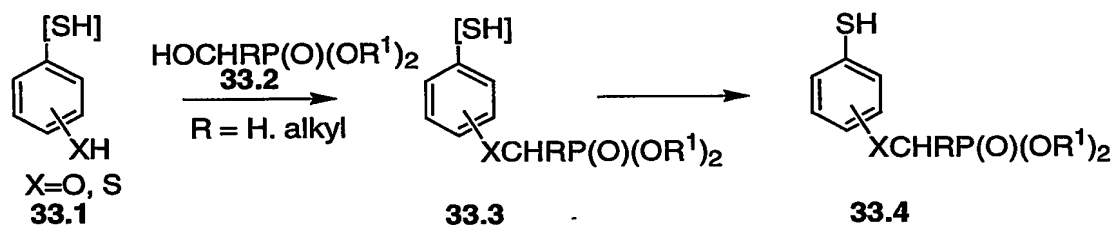
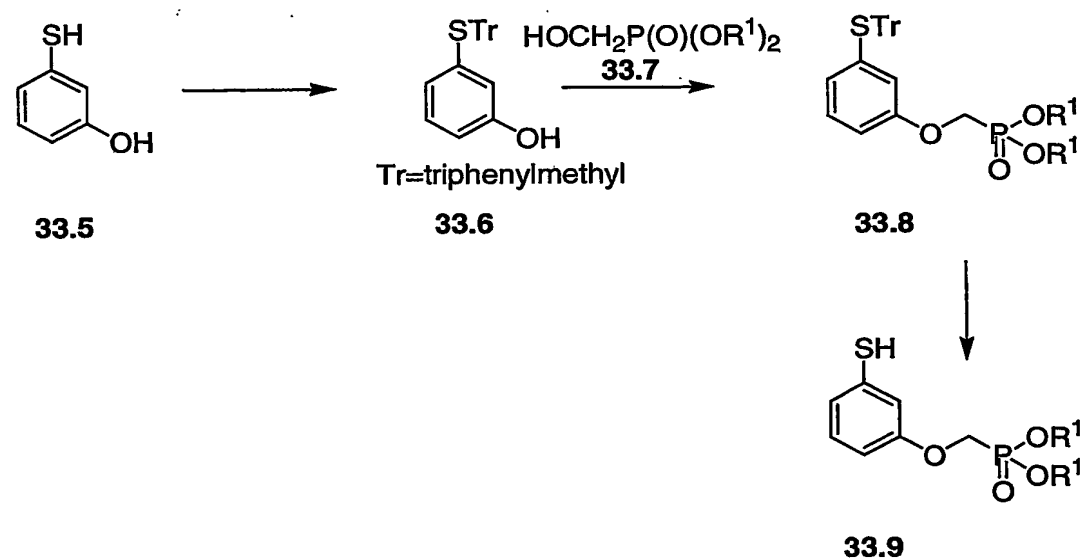
15 Scheme 39 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

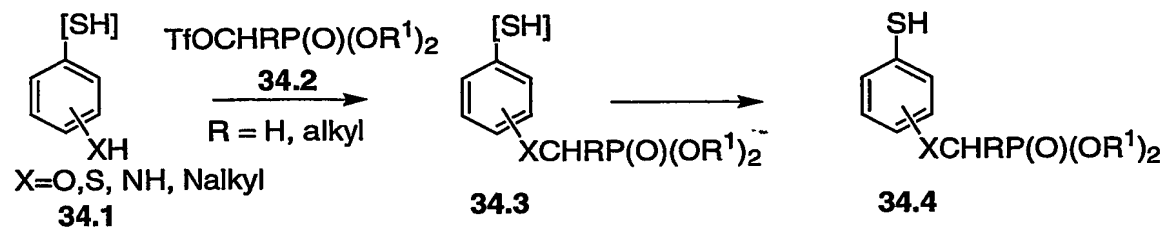
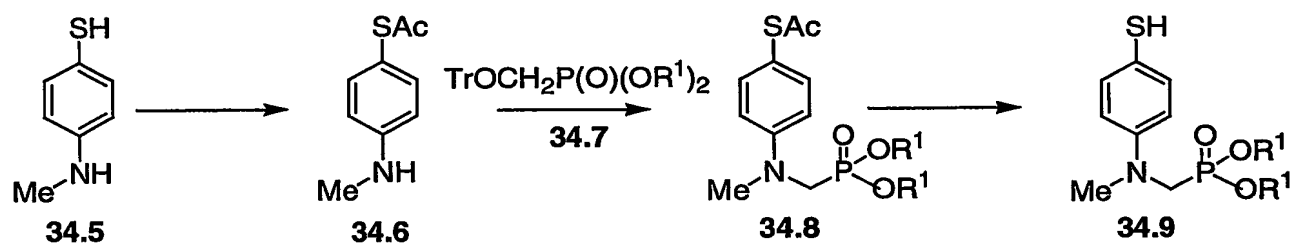
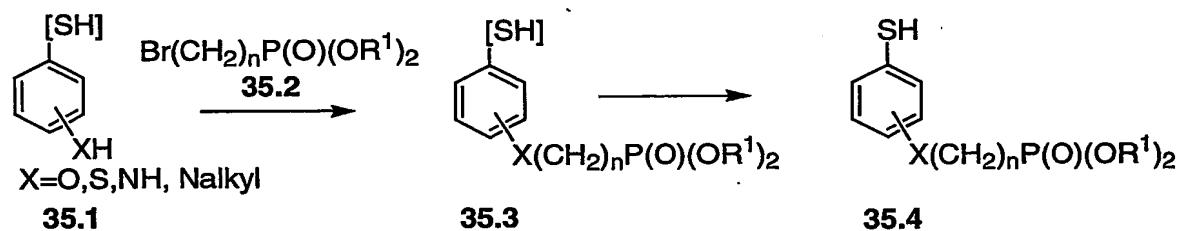
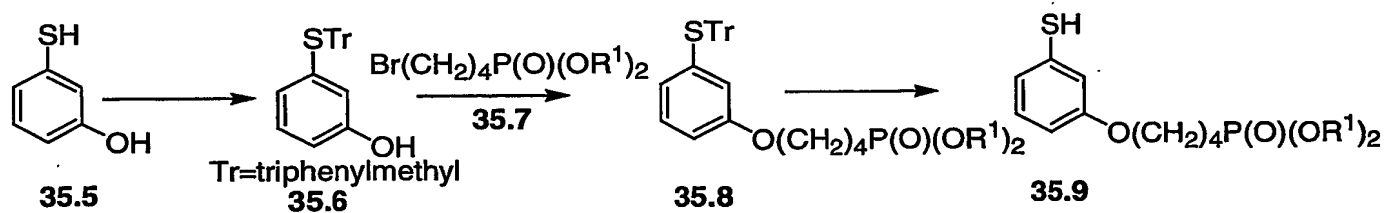
In this procedure, a suitably protected thiophenol 39.1, for example an indoline (in which X-Y is (CH₂)₂), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH₂)₃) is reacted
20 with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 39.2, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 39.3. Deprotection, as described above, then affords the thiol 39.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the
25 corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in
30 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived

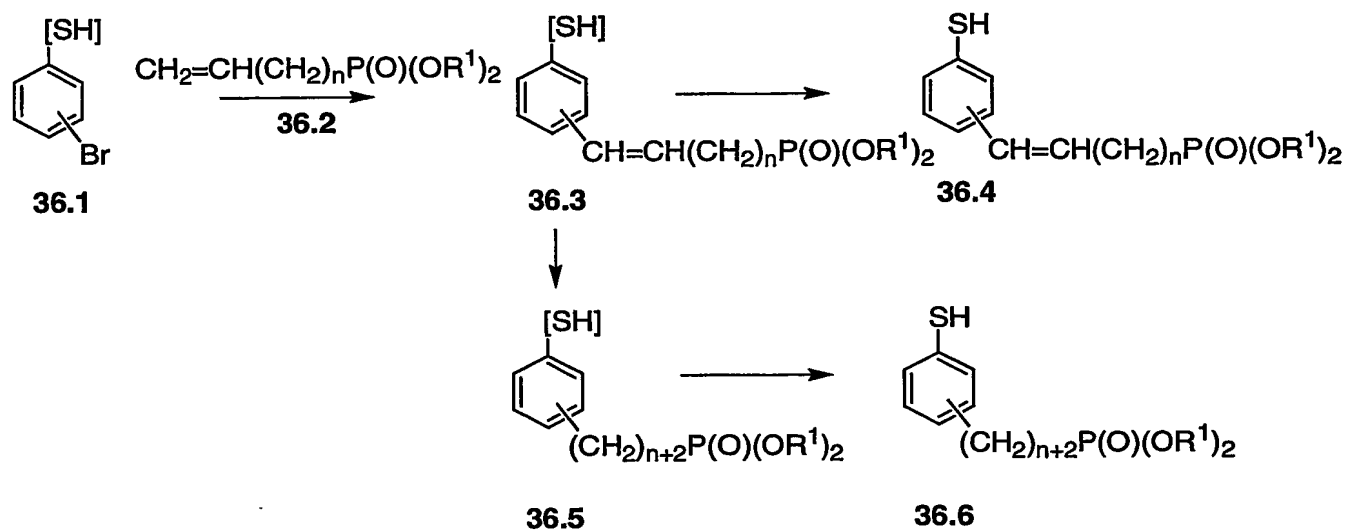
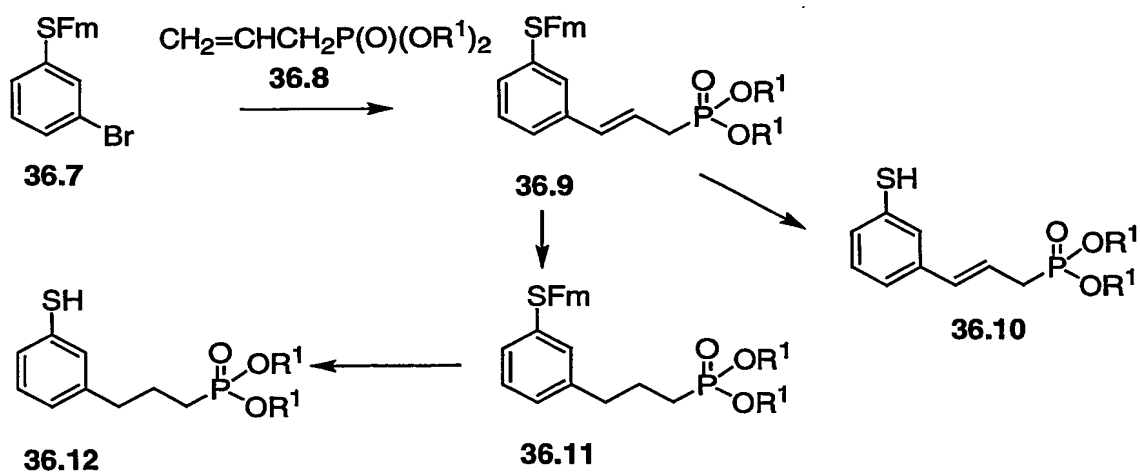
organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **39.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **39.6**, as described above, and the ester is then
5 reacted with the trifluoromethanesulfonate **39.7**, using the conditions described above for the preparation of the phosphonate **34.8**, (Scheme 34), to yield the phosphonate **39.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **39.9**.

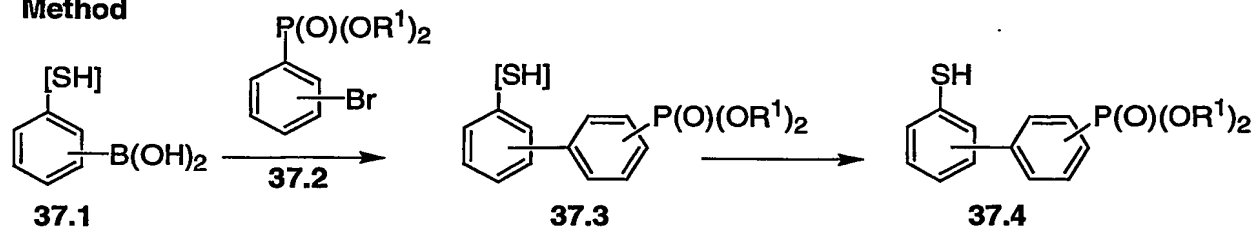
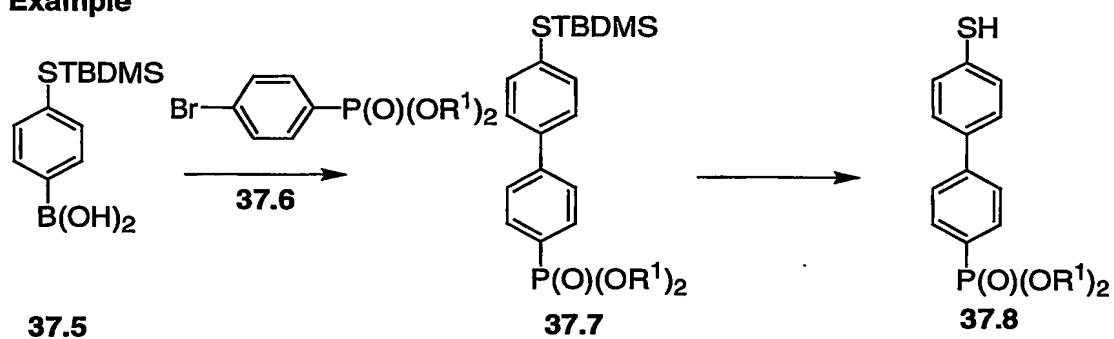
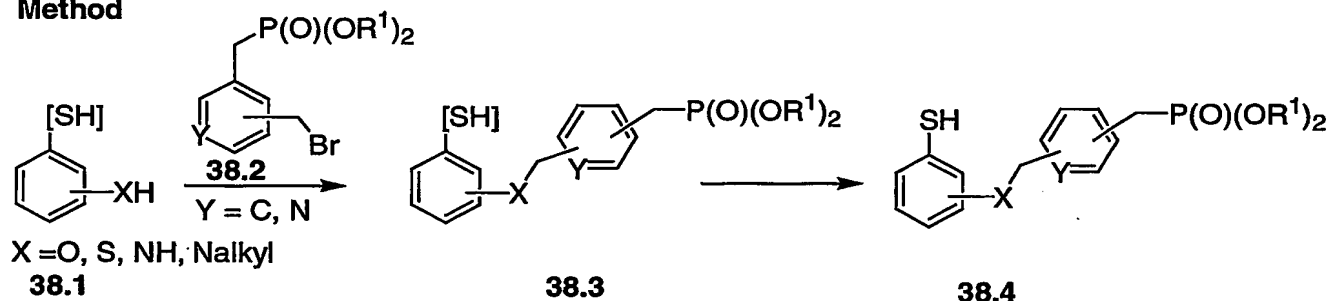
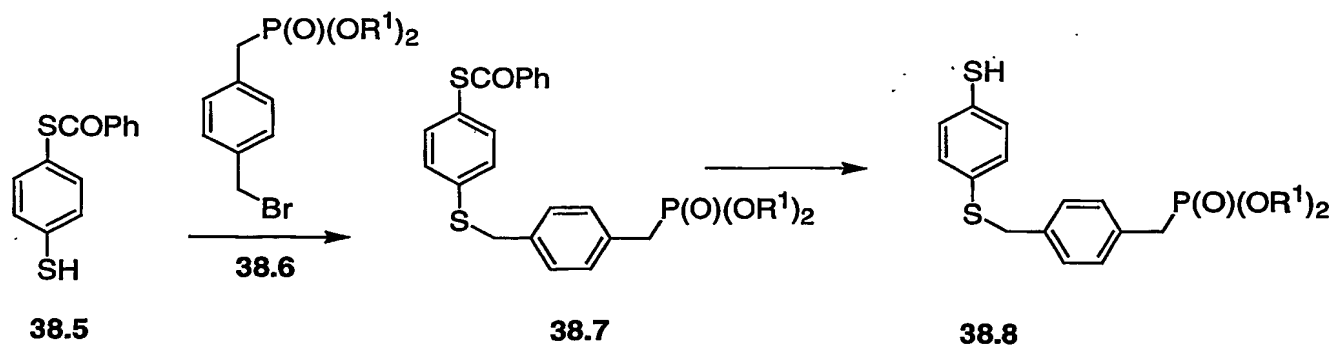
Using the above procedures, but employing, in place of the thiol **39.5**, different thiols **39.1**,
10 and/or different triflates **39.2**, there are obtained the corresponding products **39.4**.

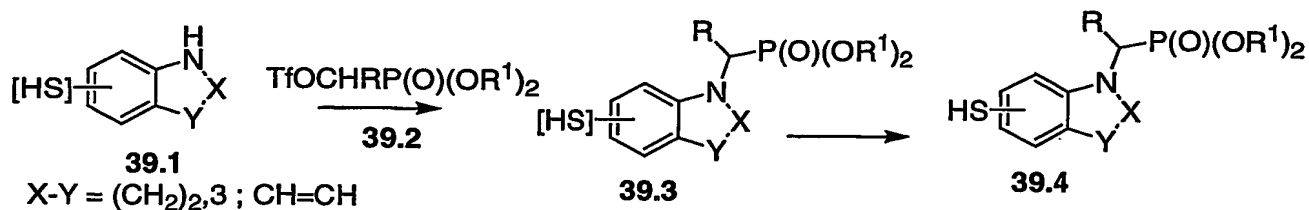
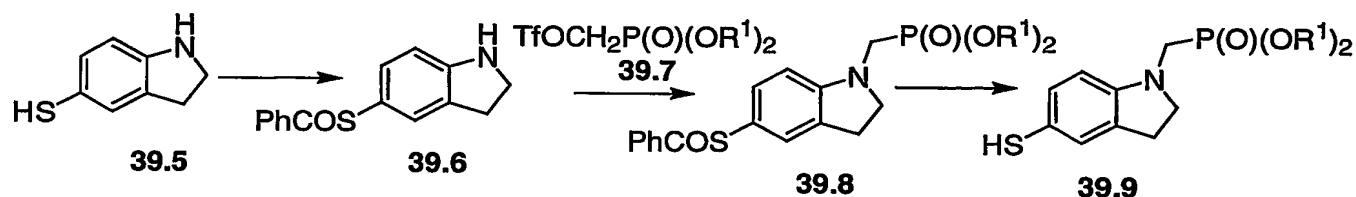
Scheme 30**Method****Example****Scheme 31****Method****Example**

Scheme 32**Method****Example****Scheme 33****Method****Example**

Scheme 34**Method****Example****Scheme 35****Method****Example**

Scheme 36**Method****Example**

Scheme 37**Method****Example****Scheme 38****Method****Example**

Scheme 39**Method****Example****Preparation of the phenylpyridylphosphonate aldehydes 4.9.**

5

Schemes **40** and **41** illustrate methods for the preparation of 4-(2-pyridyl)benzaldehydes **4.9** incorporating phosphonate groups, which are employed in the preparation of the phosphonate ester intermediates **3a**.

Scheme **40** illustrates the preparation of benzaldehydes substituted at the 4 position with a bromo-substituted 2-pyridine group, and the conversion of the bromo substituent into various phosphonate substituents, linked to the pyridine ring either directly, or by means of a saturated or unsaturated alkylene chain, or by a heteroatom and an alkylene chain.

In this procedure, a 4-formylphenylboronate **40.1** (Lancaster Synthesis) is coupled with a dibromopyridine **40.2** to afford the bromopyridyl benzaldehyde product **40.3**. Equimolar amounts of the reactants are combined in the presence of a palladium catalyst, as described above (Scheme **4**). The bromopyridine product **40.3** is then reacted with a dialkyl phosphite **40.4**, in the presence of a palladium catalyst, as described above (Scheme **27**) to afford the pyridylphosphonate ester **40.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

Alternatively, the bromopyridine compound **40.3** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **40.6**, to yield the alkenyl phosphonate **40.9**, using

the procedures described above, (Scheme 28). The olefinic bond present in the product is then reduced to afford the saturated analog **40.8**. The reduction reaction is performed catalytically, for example by the use of palladium on carbon and hydrogen or a hydrogen donor, or chemically, for example by employing diimide, generated by treatment of disodium

5 azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961.

Alternatively, the bromopyridine compound **40.3**, in which the bromo substituent is in either the 4 or 6 position, is transformed, by reaction with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate **40.7**, into the ether, thioether or amine product **40.10**. The preparation of

10 bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41

respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100° in the presence of a base such as potassium carbonate, to effect the displacement reaction.

15 Scheme 40, Example 1, illustrates the coupling reaction of 4-formylphenylboronic acid **40.1** with 2,5-dibromopyridine **40.11**, using the procedure described above, to afford 4-(5-bromo-2-pyridyl)benzaldehyde **40.12**. This compound is then coupled, as described above, with a dialkyl phosphite **40.4**, to afford the pyridyl phosphonate **40.13**.

Using the above procedures, but employing, in place of 2,5-dibromopyridine **40.11**, different
20 dibromopyridines **40.2**, and/or different dialkyl phosphites **40.4**, the corresponding products **40.5** are obtained.

Alternatively, as illustrated in Scheme 40, Example 2, the phenylboronic acid **40.1** is coupled, as described above, with 2,4-dibromopyridine **40.14** to afford 4-(4-bromo-2-pyridyl)benzaldehyde **40.15**. The product is then reacted with a dialkyl mercaptoethyl
25 phosphonate **40.16**, the preparation of which is described in Zh. Obschei. Khim., 1973, 43, 2364, to yield the thioether **40.17**. Equimolar amounts of the reactants are combined in dimethylformamide at 80° in the presence of potassium carbonate, to effect the displacement reaction.

Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate
30 **40.16**, different dialkyl hydroxy, mercapto or aminoalkyl phosphonates **40.7**, the corresponding products **40.10** are obtained.

Alternatively, as shown in Scheme 40, Example 3, 4-(5-bromo-2-pyridyl)benzaldehyde 40.12 is coupled with a dialkyl vinyl phosphonate 40.18, in the presence of a palladium catalyst, as described above, to afford the unsaturated phosphonate 40.19. Optionally, the product can be reduced to the saturated analog 40.20, for example by the use of diimide, as described above.

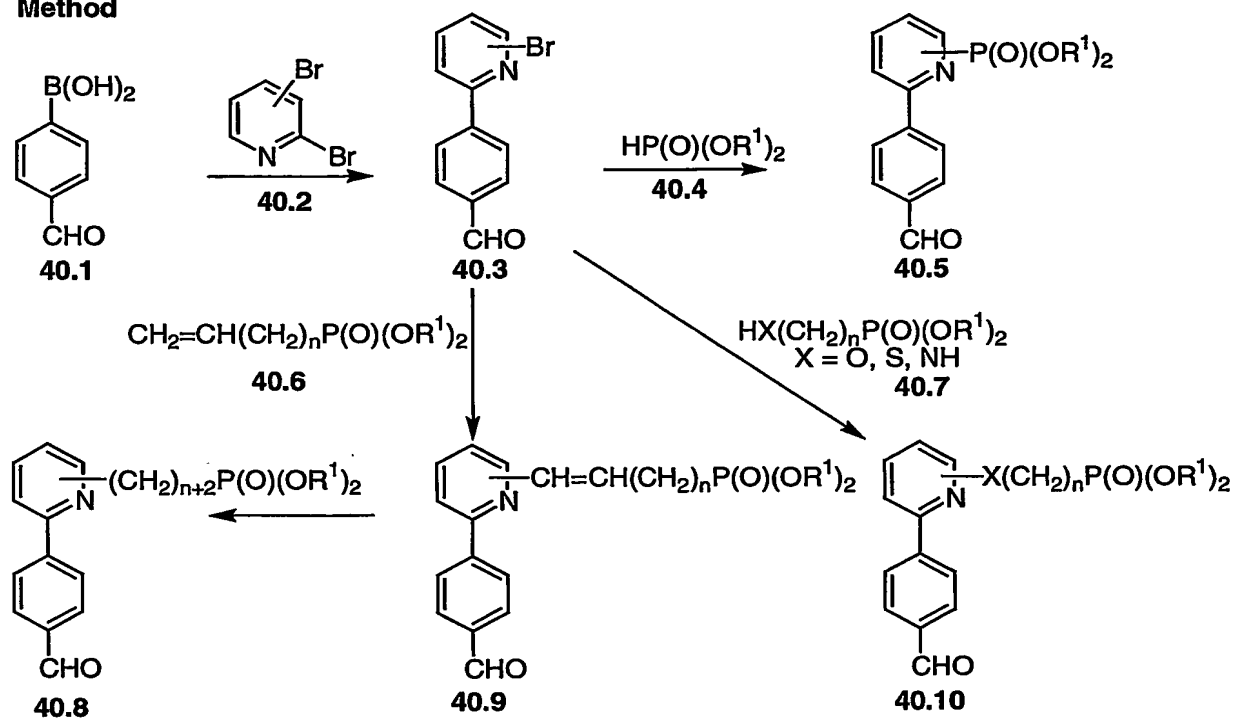
- 5 Using the above procedures, but employing, in place of the bromoaldehyde 40.12, different bromoaldehydes 40.3, and/or, in place of the dialkyl vinylphosphonate 40.18, different dialkyl alkenylphosphonates 40.6, the corresponding products 40.8 and 40.9 are obtained.

- Scheme 41 illustrates the preparation of 4-(2-pyridyl)benzaldehydes incorporating phosphonate group linked by means of a alkylene chain incorporating a nitrogen atom. In this
10 procedure, a formyl-substituted 2-bromopyridine 41.2 is coupled, as described above, (Scheme 40) with a 4-(hydroxymethyl)phenylboronic acid 41.1. prepared as described in Macromolecules, 2001, 34, 3130, to afford the 4-(2-pyridyl)benzyl alcohol 41.3. The product is then reacted with a dialkyl aminoalkyl phosphonate 41.4, under reductive amination
15 conditions. The preparation of amines by means of a reductive amination of an aldehyde is described above (Scheme 24). The resultant benzyl alcohol 41.5 is then oxidized to yield the corresponding benzaldehyde 41.6. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate,
20 silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. Preferably, the alcohol 41.5 is oxidized to the aldehyde 41.6 by reaction with pyridinium chlorochromate in dichloromethane.

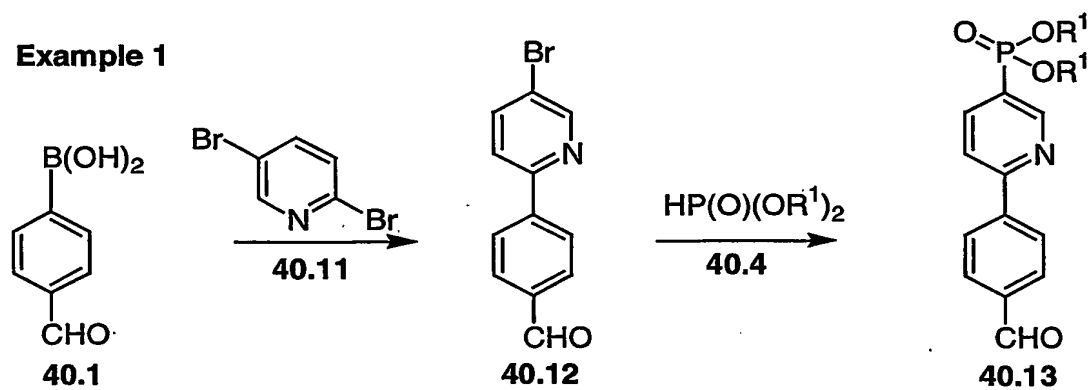
- For example, the phenylboronic acid 41.1 is coupled with 2-bromopyridine-4-carboxaldehyde 41.7, the preparation of which is described in Tet. Lett. 2001, 42, 6815, to afford 4-(4-formyl-
25 2-pyridyl)benzyl alcohol 41.8. The aldehyde is then reductively aminated by reaction with a dialkyl aminoethylphosphonate 41.9, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and a reducing agent, to afford the amine product 41.10. The latter compound is then oxidized, for example by treatment with pyridinium chlorochromate, to afford the aldehyde phosphonate 41.11.

- 30 Using the above procedures, but employing, in place of the bromopyridine aldehyde 41.7, different aldehydes 41.2, and/or different dialkyl aminoalkyl phosphonates 41.4, the corresponding products 41.6 are obtained.

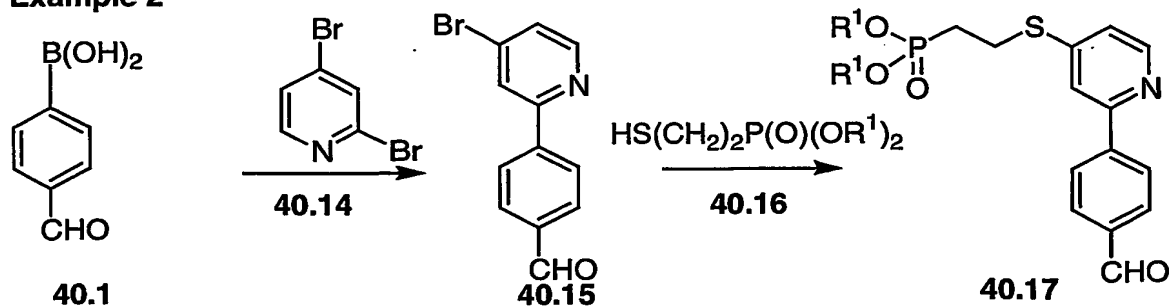
Scheme 40 Method

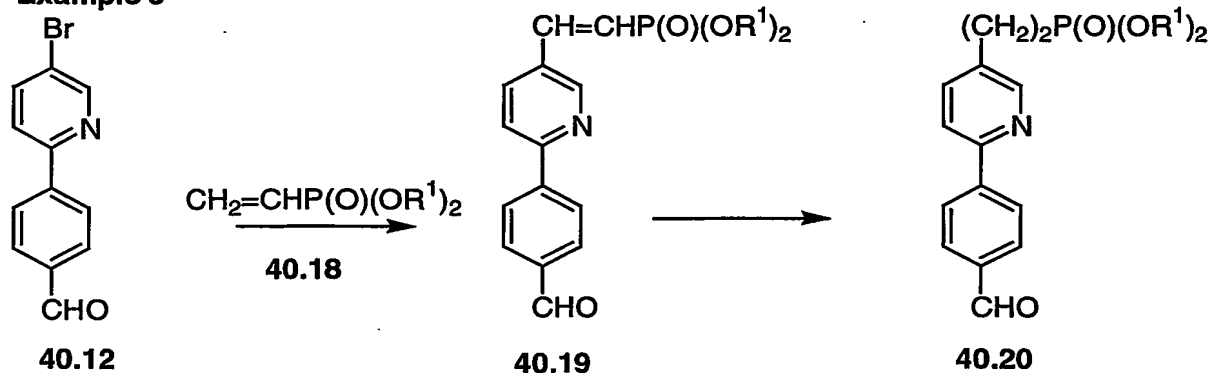
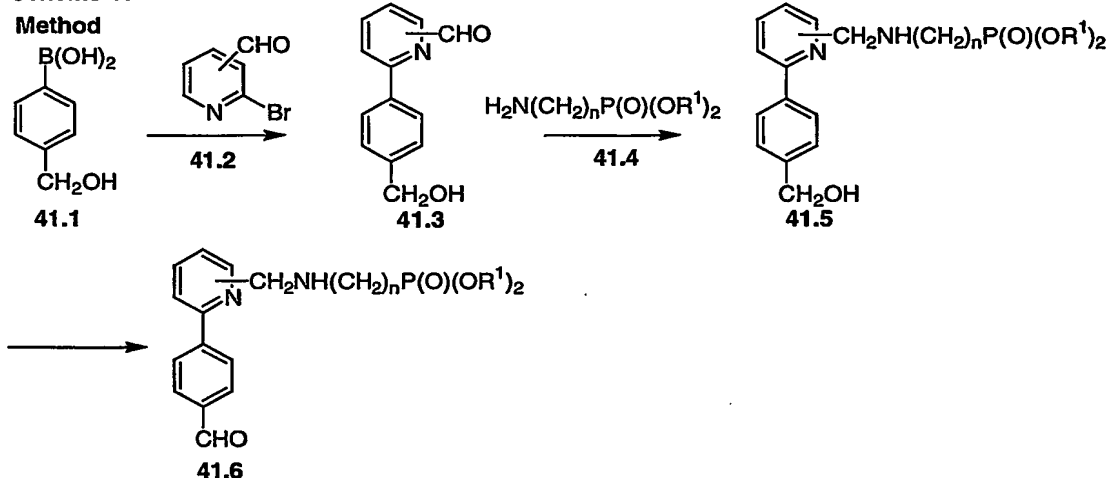
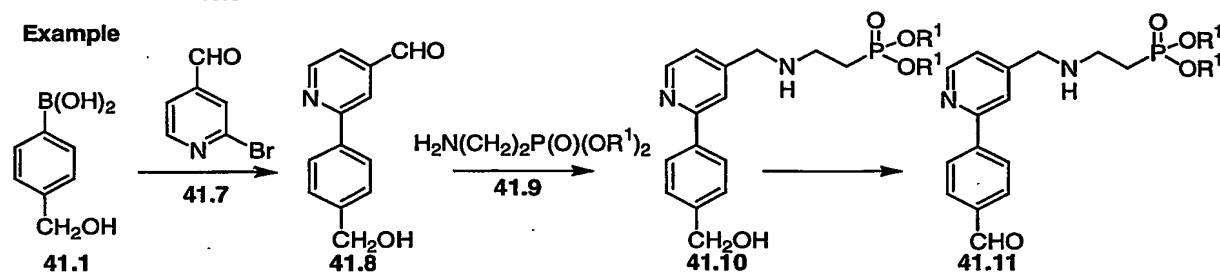


Example 1



Example 2



Example 3**Scheme 41****Example****5 Preparation of the biphenyl phosphonate aldehydes 4.12.**

Schemes 42 - 44 illustrate methods for the preparation of the biphenylphosphonate aldehydes **4.12** which are employed in the synthesis of the phosphonate esters **3b**.

Scheme 42 depicts the preparation of biphenyl aldehyde phosphonates in which the phosphonate moiety is attached to the phenyl ring either directly, or by means of a saturated or unsaturated alkylene chain. In this procedure, 4-formylbenzeneboronic acid **42.1** and a

dibromobenzene **42.2** are coupled in the presence of a palladium catalyst, as described above, to produce the bromobiphenyl aldehyde **42.3**. The aldehyde is then coupled, as described above, with a dialkyl phosphite **42.4**, to afford the phosphonate ester **42.5**. Alternatively, the bromoaldehyde **42.3** is coupled with a dialkyl alkenylphosphonate **42.6**, using the procedures described above, to afford the alkenyl phosphonate **42.8**. Optionally, the latter compound is reduced to yield the saturated analog **42.7**.

For example, as shown in Scheme **42**, Example 1, 4-formylbenzeneboronic acid **42.1** is coupled with 1,3-dibromobenzene **42.9** to give 3'-bromo-4-formylbiphenyl **42.10**. The product is then coupled, as described above, with a dialkyl phosphite **42.4** to give the biphenyl phosphonate ester **42.11**.

Using the above procedures, but employing, in place of 1,3-dibromobenzene **42.9**, different dibromobenzenes **42.2**, and/or different dialkyl phosphites **42.4**, the corresponding products **42.5** are obtained.

As a further example of the methods of Scheme **42**, as shown in Example 2, 4'-bromobiphenyl-4-aldehyde **42.12** is coupled with a dialkyl propenylphosphonate **42.13** (Aldrich) in the presence of a palladium catalyst, to produce the propenyl phosphonate **42.15**. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated product **42.16**.

Using the above procedures, but employing, in place of the 4-bromobiphenyl aldehyde **42.12**, different bromobiphenyl aldehydes, and/or different alkenyl phosphonates **42.6**, the corresponding products **42.7** and **42.8** are obtained.

Scheme **43** illustrates the preparation of biphenyl phosphonates in which the phosphonate group is attached by means of a single carbon or by a heteroatom O, S or N and an alkylene chain. In this procedure, a bromotoluene **43.2** is coupled with 4-formylbenzeneboronic acid **43.1** to yield the methyl-substituted biphenyl aldehyde **43.3**. The product is then subjected to a free radical bromination to produce the bromomethyl compound **43.4**. The conversion of aromatic methyl groups into the corresponding benzylic bromide is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. The transformation is effected, for example, by the use of bromine, N-bromosuccinimide, carbon tetrabromide or bromotrichloromethane. The reaction is performed in an inert organic solvent such as carbon tetrachloride, ethyl acetate and the like, at reflux temperature, optionally in the

presence of an initiator such as dibenzoyl peroxide. Preferably, the conversion of the methyl compound 43.3 to the bromomethyl product 43.4 is effected by the use of one molar equivalent of N-bromosuccinimide in refluxing carbon tetrachloride. The bromomethyl compound is then reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate product 43.6. The displacement reaction is performed in an inert solvent such as tetrahydrofuran, at from ambient temperature to reflux, as described in J. Med. Chem., 1992, 35, 1371.

Alternatively, the bromomethyl compound 43.4 is reacted with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate 43.7 to prepare the corresponding ether, thioether or aminoalkyl phosphonate products 43.8. The reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, at from ambient temperature to about 80°, in the presence of an inorganic or organic base. For the preparation of the ethers 43.8 in which X is O, a strong base such as sodium hydride or potassium tert. butoxide is employed. For the preparation of the thioethers or amines 43.8, a base such as cesium carbonate,

dimethylaminopyridine or diisopropylethylamine is employed.

Scheme 43, Example 1 depicts the coupling reaction of 4-formylbenzeneboronic acid 43.1 with 3-bromotoluene 43.9 to afford 3'-methylbiphenyl-4-aldehyde 43.10. The product is then reacted with N-bromosuccinimide, as described above, to afford the bromomethyl product 43.11. This material is reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate ester 43.12.

Using the above procedures, but employing, in place of 3-bromotoluene 43.9, different bromotoluenes 43.2, the corresponding products 43.6 are obtained.

Scheme 43, Example 2 shows the free-radical bromination of 4'-methylbiphenyl-4-aldehyde to give the 4'-bromomethylbiphenyl-4-aldehyde 43.14. The product is then reacted in acetonitrile solution at 70° with one molar equivalent of a dialkyl aminoethyl phosphonate 43.15, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and cesium carbonate, to yield the amine product 43.16.

Using the above procedures, but employing, in place of the aminoethyl phosphonate 43.15, different hydroxy, mercapto or aminoalkyl phosphonates 43.7, and/or different biphenyl aldehydes 43.3, the corresponding products 43.8 are obtained.

Scheme 44 illustrates the preparation of the biphenyl phosphonates 44.3 in which the phosphonate group is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted biphenyl aldehyde 44.1 is reacted with a dialkyl bromoalkyl phosphonate 44.2 to afford the alkylation product 44.3. The reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide and the like, at from ambient temperature to about 80°, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of an inorganic iodide such as potassium iodide.

For example, 3'-hydroxybiphenyl-4-aldehyde 44.4 is reacted with a dialkyl bromoethyl phosphonate 44.5 (Aldrich) and potassium carbonate in dimethylformamide at 80°, to produce the ether 44.6.

Using the above procedures, but employing, in place of 3'-hydroxybiphenyl-4-aldehyde 44.4, different hydroxy, mercapto or aminobiphenyl-4-aldehydes 44.1, and/or different bromoalkyl phosphonates 44.2, the corresponding products 44.3 are obtained.

Preparation of the benzaldehyde phosphonates 4.14.

Schemes 45 - 48 illustrate methods for the preparation of the benzaldehyde phosphonates 4.14 which are employed in the synthesis of the phosphonate esters 3d.

Scheme 45 illustrates the preparation of benzaldehyde phosphonates 45.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 45.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 45.2, under reductive amination conditions, as describe above in Scheme 24, to yield the phosphonate product 45.3.

For example, benzene-1,3-dialdehyde 45.4 is reacted with a dialkyl aminopropyl phosphonate 45.5, (Acros) and sodium triacetoxyborohydride, to afford the product 45.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 45.4, different benzene dialdehydes 45.1, and/or different phosphonates 45.2, the corresponding products 45.3 are obtained.

Scheme 46 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this

procedure, a bromobenzaldehyde **46.1** is coupled, under palladium catalysis as described above, with a dialkyl alkenylphosphonate **46.2**, to afford the alkenyl phosphonate **46.3**. Optionally, the product can be reduced, as described above, to afford the saturated phosphonate ester **46.4**. Alternatively, the bromobenzaldehyde can be coupled, as described
5 above, with a dialkyl phosphite **46.5** to afford the formylphenylphosphonate **46.6**. For example, as shown in Example 1, 3-bromobenzaldehyde **46.7** is coupled with a dialkyl propenylphosphonate **46.8** to afford the propenyl product **46.9**. Optionally, the product is reduced to yield the propyl phosphonate **46.10**.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde **46.7**, different
10 bromobenzaldehydes **46.1**, and/or different alkenyl phosphonates **46.2**, the corresponding products **46.3** and **46.4** are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde **46.11** is coupled with a dialkyl phosphite **46.5** to afford the 4-formylphenyl phosphonate product **46.12**.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde **46.11**, different
15 bromobenzaldehydes **46.1**, the corresponding products **46.6** are obtained.

Scheme 47 illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or
20 alkylamine **47.1** is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate **47.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **47.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **47.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium
25 hexamethyldisilazide is employed. In cases in which Y is O or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **47.4**, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl
iodomethyl phosphonate **47.5**, (Lancaster) to give the ether product **47.6**.

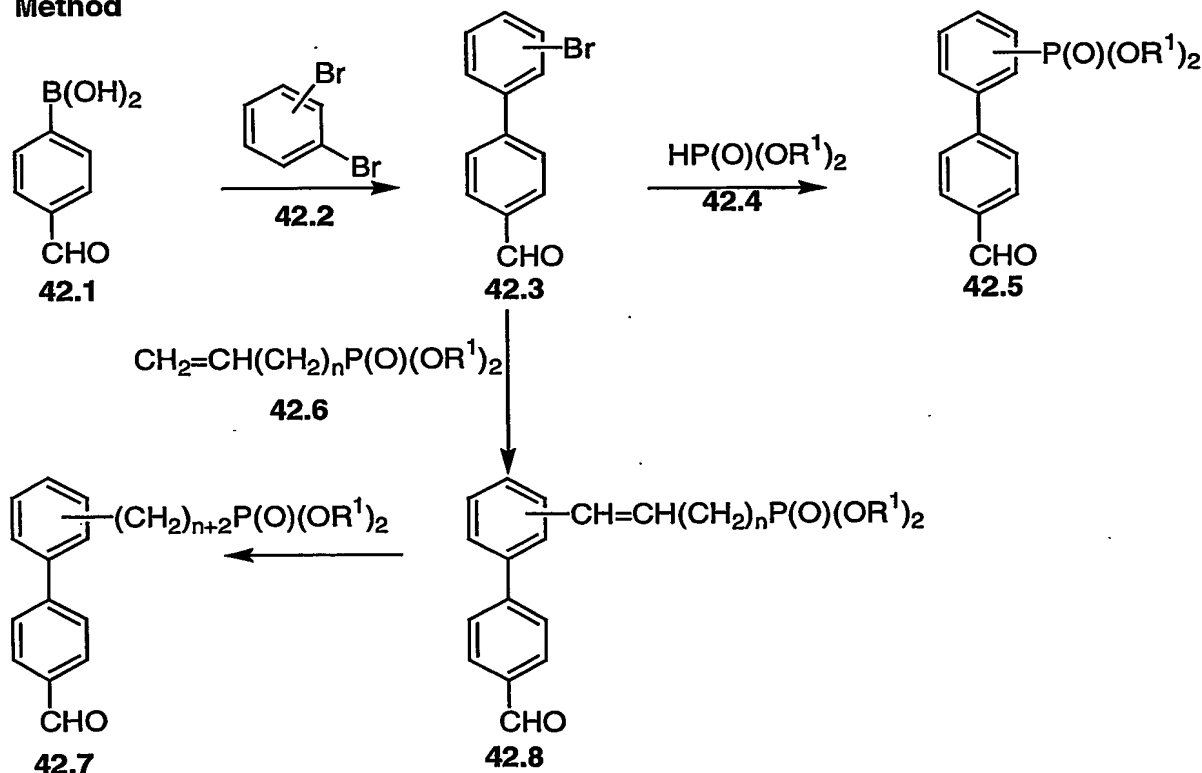
Using the above procedures, but employing, in place of the carbinol **47.4**, different carbinols,
30 thiols or amines **47.1**, and/or different haloalkyl phosphonates **47.2**, the corresponding products **47.3** are obtained.

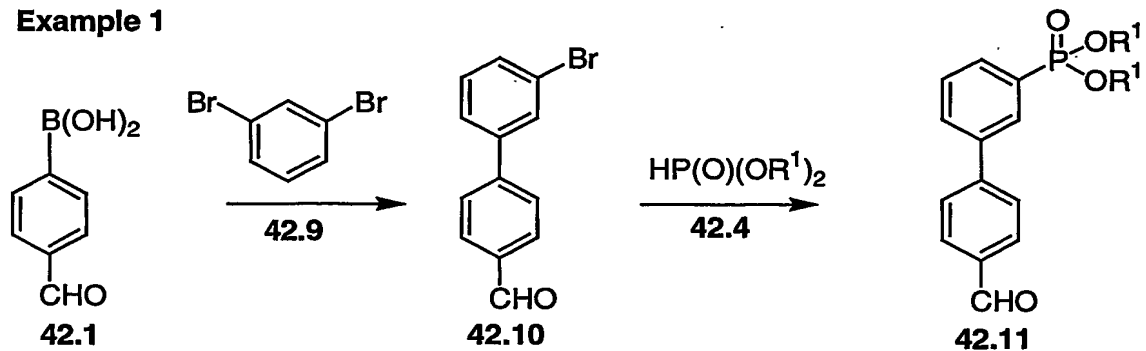
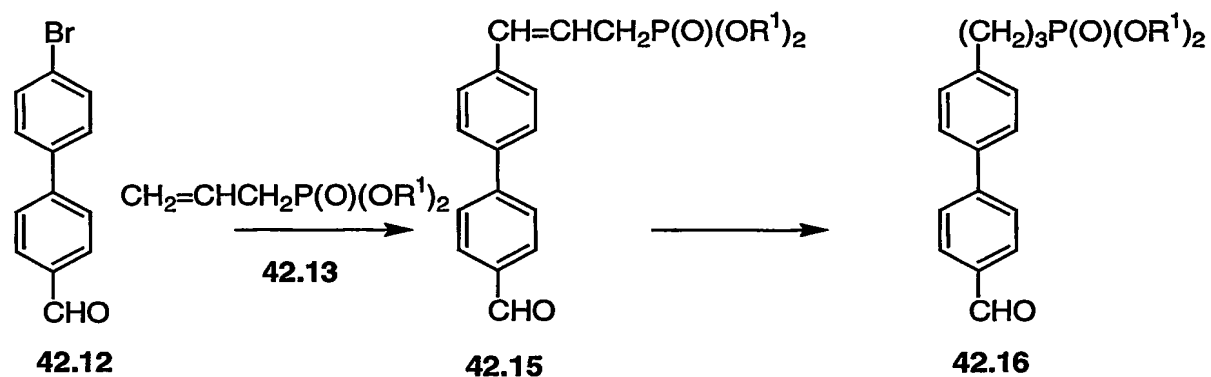
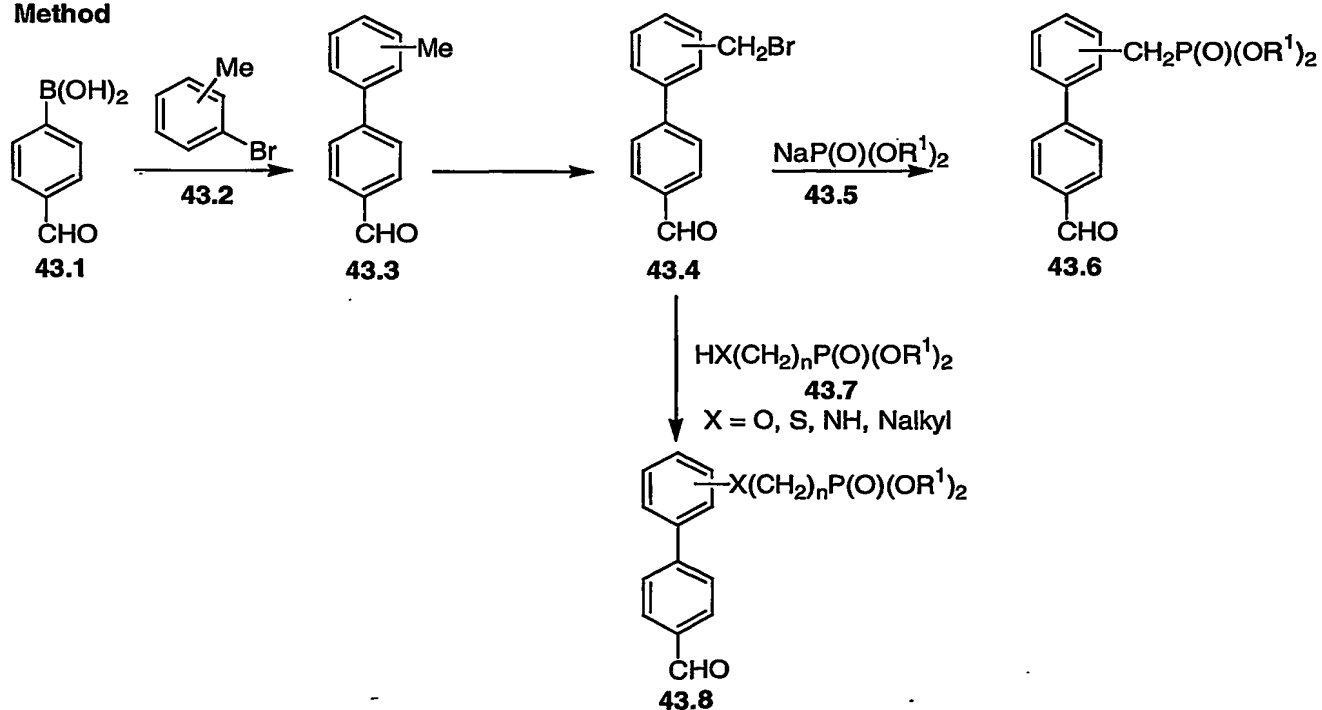
Scheme 48 illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, 4-formylbenzeneboronic acid **43.1** is coupled, as described previously, with one molar equivalent of a dibromoarene, **48.1**, in which the group Ar is an aromatic or heteroaromatic group. The product **48.2** is then coupled, as described above (Scheme 46) with a dialkyl phosphite **40.4** to afford the phosphonate **48.3**.

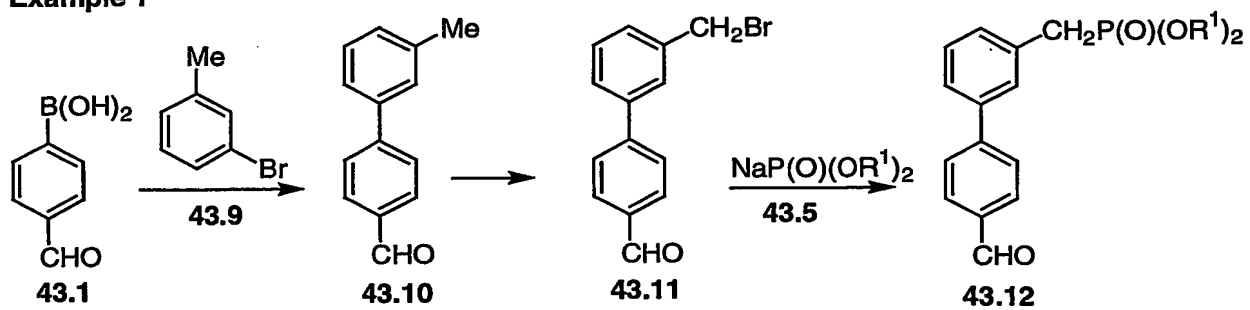
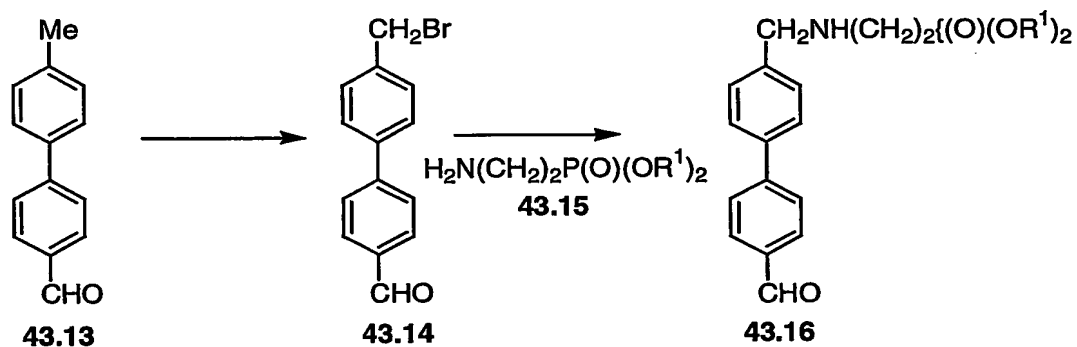
For example, 4-formylbenzeneboronic acid **43.1** is coupled with 2,5-dibromothiophene **48.4** to yield the phenylthiophene product **48.5**. This compound is then coupled with the dialkyl phosphite **40.4** to afford the thienyl phosphonate **48.6**.

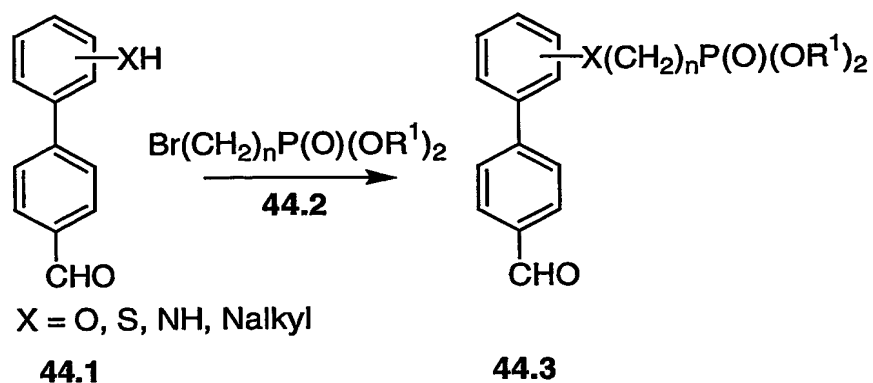
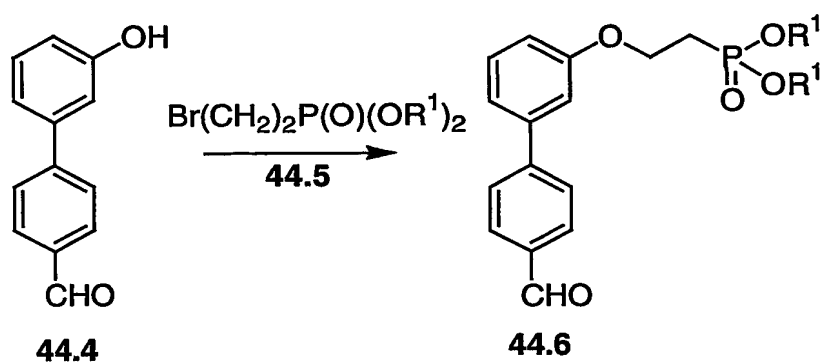
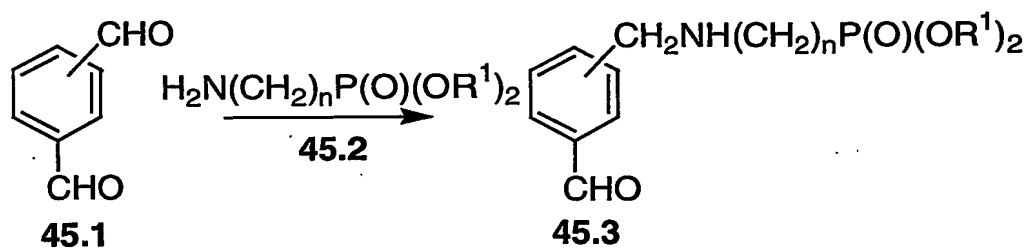
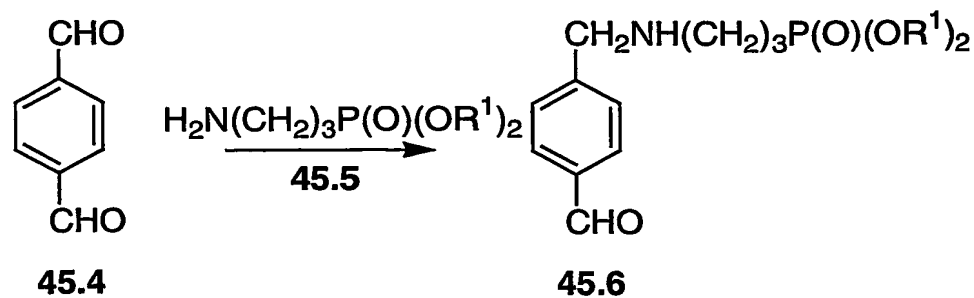
Using the above procedures, but employing, in place of dibromothiophene **48.4**, different dibromoarenes **48.1**, the corresponding products **48.3** are obtained.

Scheme 42
Method



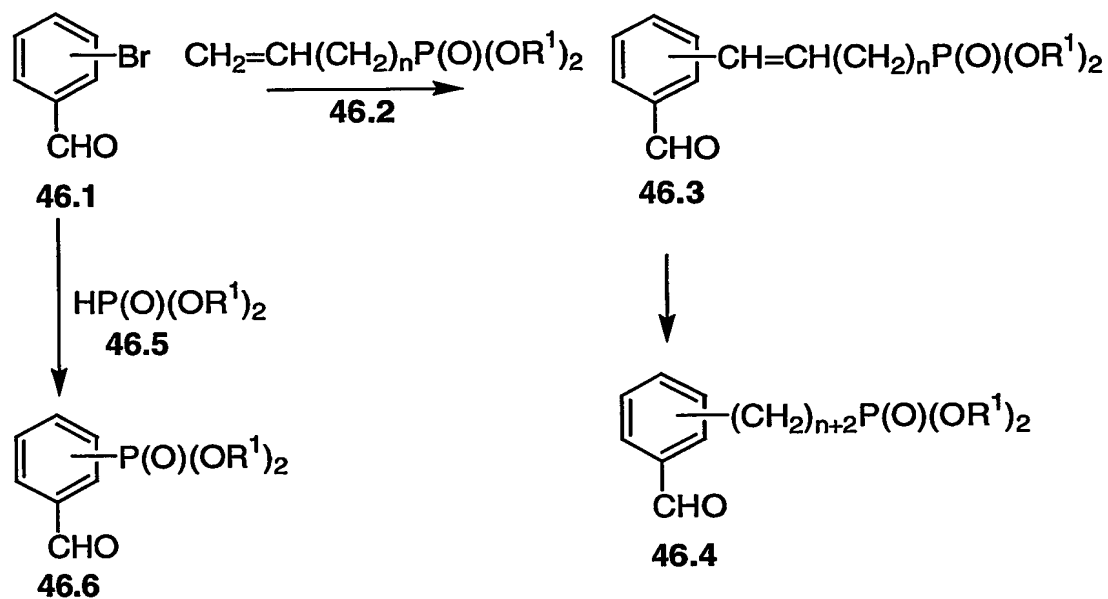
Example 1**Example 2****Scheme 43****Method**

Example 1**Example 2**

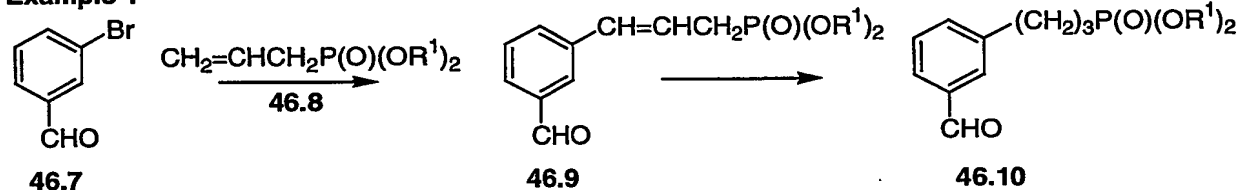
Scheme 44**Method****Example****Scheme 45****Method****Example**

Scheme 46

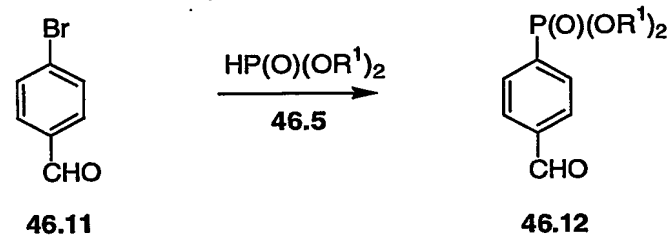
Method

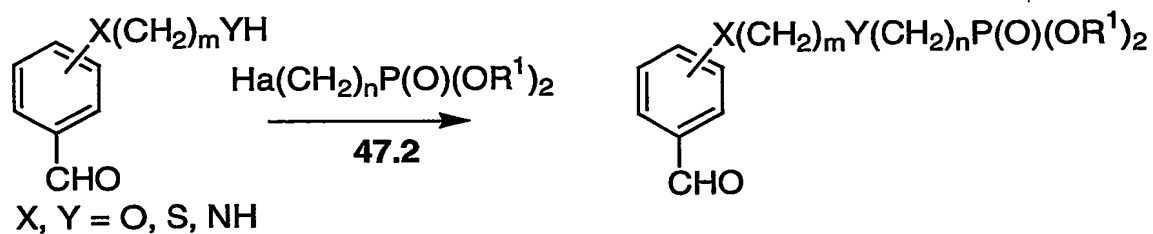
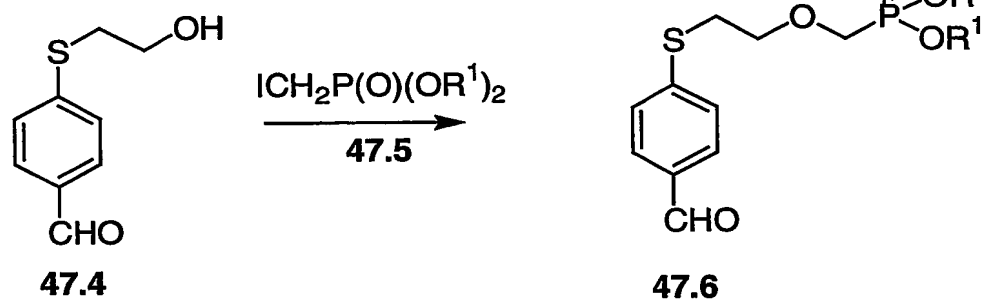
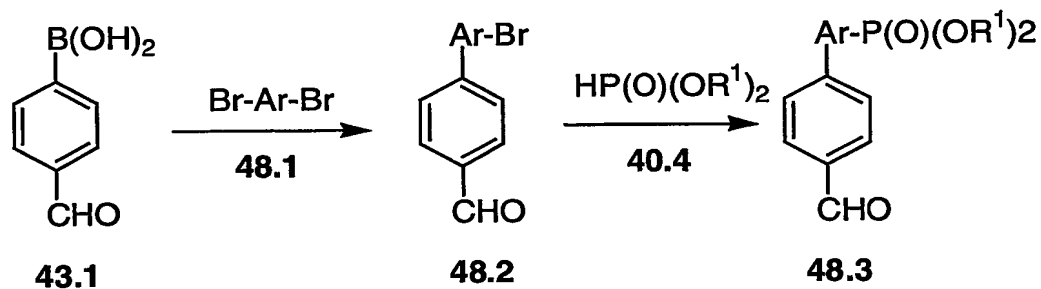
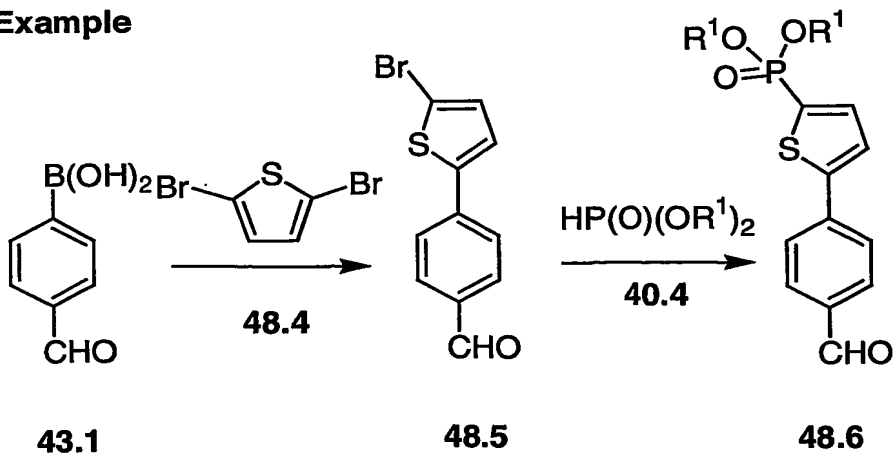


Example 1



Example 2



Scheme 47**Method****47.1****Example****Scheme 48****Method****Example**

Preparation of the cyclohexanecarboxaldehyde phosphonates 4.16.

Schemes 49 - 52 illustrate methods for the preparation of the cyclohexanecarboxaldehyde phosphonates 4.16 which are employed in the synthesis of the phosphonate esters 3c.

Scheme 49 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a nitrogen and an alkylene chain. In this procedure, a cyclohexane dicarboxaldehyde 49.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 49.2 under reductive amination conditions, as described above, to afford the phosphonate product 49.3.

For example, cyclohexane-1,3-dialdehyde 49.4, the preparation of which is described in J. Macromol. Sci. Chem., 1971, 5, 1873, is reacted with a dialkyl aminopropyl phosphonate 49.5, (Acros) and one molar equivalent of sodium triacetoxyborohydride, to yield the phosphonate product 49.6.

Using the above procedures, but employing, in place of cyclohexane-1,3-dialdehyde 49.4, different cyclohexane dialdehydes 49.1, and /or different aminoalkyl phosphonates 49.2, the corresponding products 49.3 are obtained.

Scheme 50 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a vinyl or ethylene group and a phenyl ring. In this procedure, a vinyl-substituted cyclohexane carboxaldehyde 50.1 is coupled, in the presence of a palladium catalyst, as described above, (Scheme 36) with a dialkyl bromophenylphosphonate 50.2, to afford the phosphonate product 50.3. Optionally, the product is reduced to afford the ethylene-linked analog 50.4. The reduction reaction is effected catalytically, for example by the use of hydrogen in the presence of a palladium catalyst, or chemically, for example by the use of diimide.

For example, 4-vinylcyclohexanecarboxaldehyde 50.5, the preparation of which is described in WO 9935822, is coupled with a dialkyl 3-bromophenyl phosphonate 50.6, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 50.7. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product 50.8.

Using the above procedures, but employing, in place of 4-vinylcyclohexanecarboxaldehyde **50.5**, different vinylcyclohexane carboxaldehydes **50.1**, and /or different bromophenyl phosphonates **50.2**, the corresponding products **50.3** and **50.4** are obtained.

5 Scheme **51** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of an alkylene chain incorporating an oxygen atom. In this procedure, a hydroxymethyl-substituted cyclohexane carboxaldehyde **51.1** is reacted, in the presence of a strong base such as sodium hydride or potassium tert. butoxide, with one molar equivalent of a dialkyl bromoalkyl phosphonate **51.2**, to prepare the phosphonate **51.3**. The
10 alkylation reaction is conducted in a polar organic solvent such as dimethylformamide, tetrahydrofuran or acetonitrile, at from ambient temperature to about 60°.

For example, 3-(hydroxymethyl)cyclohexanecarboxaldehyde **51.4**, prepared as described in WO 0107382, is treated with one molar equivalent of sodium hydride in tetrahydrofuran at 50°, and one molar equivalent of a dialkyl bromoethyl phosphonate **51.5** (Aldrich) to afford
15 the alkylation product **51.6**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)cyclohexanecarboxaldehyde **51.4** different hydroxymethylcyclohexane carboxaldehydes **51.1**, and /or different bromoalkyl phosphonates **51.2**, the corresponding products **51.3** are obtained.

20 Scheme **52** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is directly attached to the cyclohexane ring. In this procedure, a hydroxy-substituted cyclohexanecarboxaldehyde **52.1** is converted into the corresponding bromo derivative **52.2**. The conversion of alcohols into the corresponding bromides is described, for example, in
25 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. The transformation is effected by treatment of the alcohol with hydrobromic acid, or by reaction with hexabromoethane and triphenylphosphine, as described in Synthesis, 139, 1983. The resulting bromo compound **52.2** is then subjected to an Arbuzov reaction, by treatment with a trialkyl phosphite **52.3** at ca 100°. The preparation of phosphonates by mean of the
30 Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115. For example, 4-hydroxycyclohexanecarboxaldehyde **52.5** is reacted with one molar equivalent of hexabromoethane and triphenyl phosphine in dichloromethane, to yield 4-

bromocyclohexanecarboxaldehyde **52.6**. The product is heated at 100° with a trialkyl phosphite **52.3** to afford the cyclohexyl phosphonate **52.7**.

Using the above procedures, but employing, in place of 4-

(hydroxymethyl)cyclohexanecarboxaldehyde **52.5**, different hydroxy-substituted

5 cyclohexanecarboxaldehydes **52.1**, the corresponding products **52.4** are obtained.

Preparation of quinoline 2-carboxylic acids 19a.1 incorporating phosphonate moieties or precursors thereto.

10 The reaction sequence depicted in Schemes **19a - 19d** require the use of a quinoline-2-carboxylic acid reactant **19a.1** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino
15 and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described,
20 for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

25 Scheme **53** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **53.1** is reacted with an alkyl pyruvate ester **53.2**, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **53.3**. Hydrolysis of the ester, for example by the use of aqueous base, then
30 afford the corresponding carboxylic acid **53.4**. The carboxylic acid product **53.4** in which X is NH₂ can be further transformed into the corresponding compounds **53.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The

conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the
5 diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **53.6**, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic
10 Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **53.6**, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol **53.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **53.3** instead
15 of the carboxylic acids **53.5**.

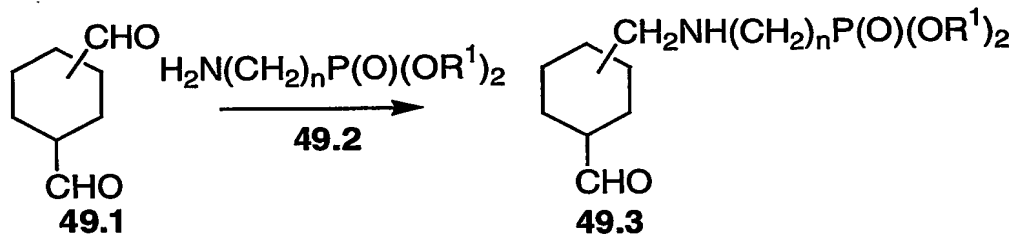
For example, 2,4-diaminobenzaldehyde **53.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **53.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **53.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the
20 carboxylic acid **53.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate **53.10** by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **53.11**, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-
25 bromoquinoline-2-carboxylic acid **53.11**, X = Br. Alternatively, the diazonium tetrafluoroborate **53.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **53.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **53.7**,
30 different aminobenzaldehydes **53.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **53.6** are obtained. The variously substituted quinoline

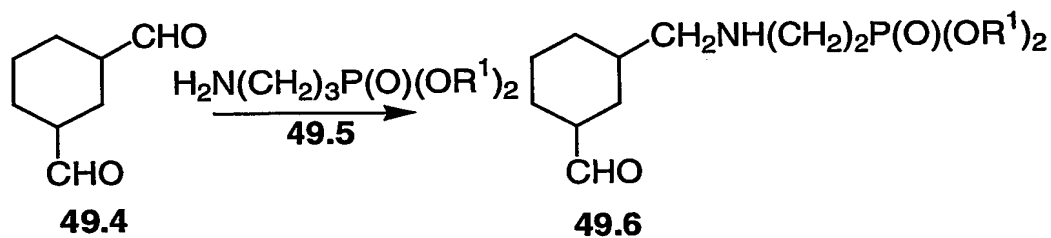
carboxylic acids and esters can then be transformed, as described below, (Schemes 54 – 56) into phosphonate-containing derivatives.

Scheme 49

Method



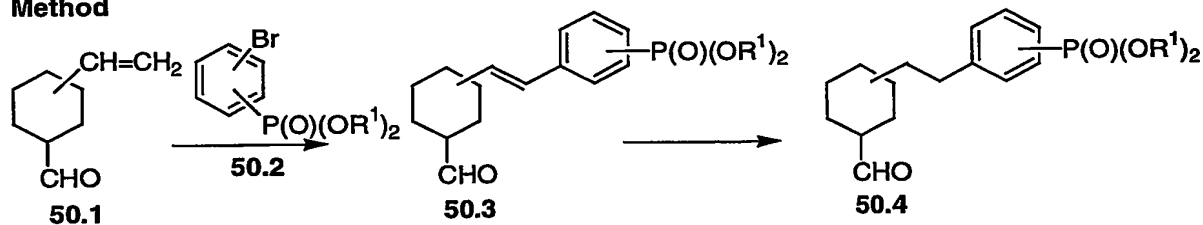
Example



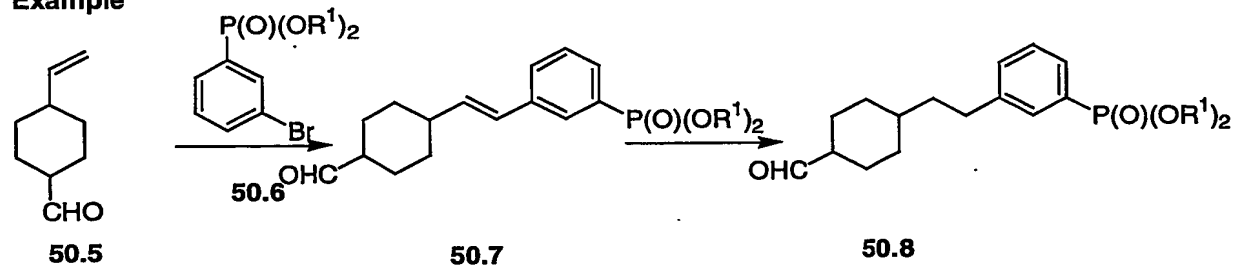
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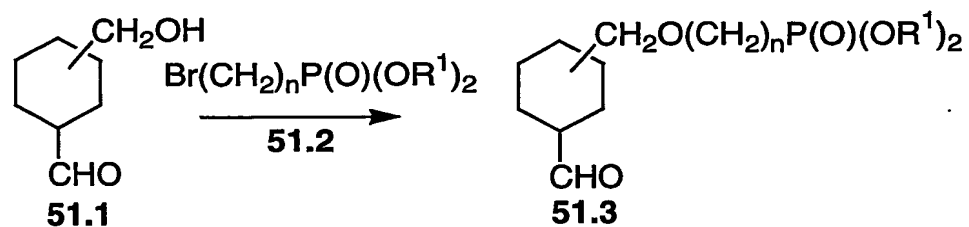
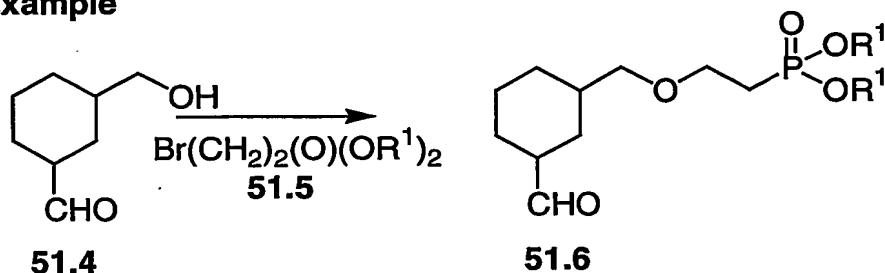
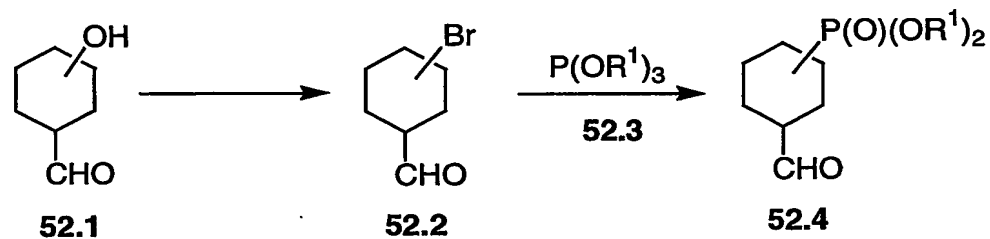
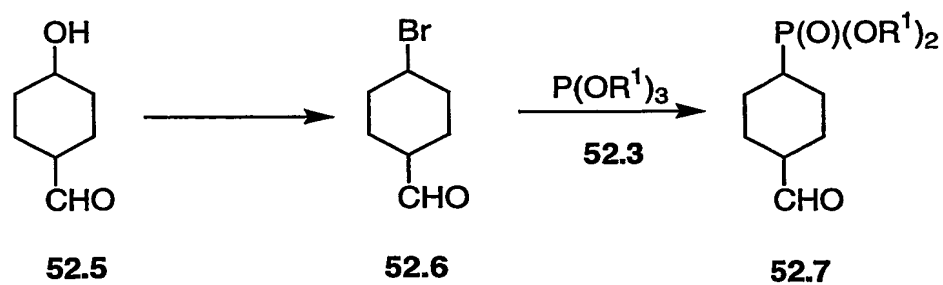
Scheme 50

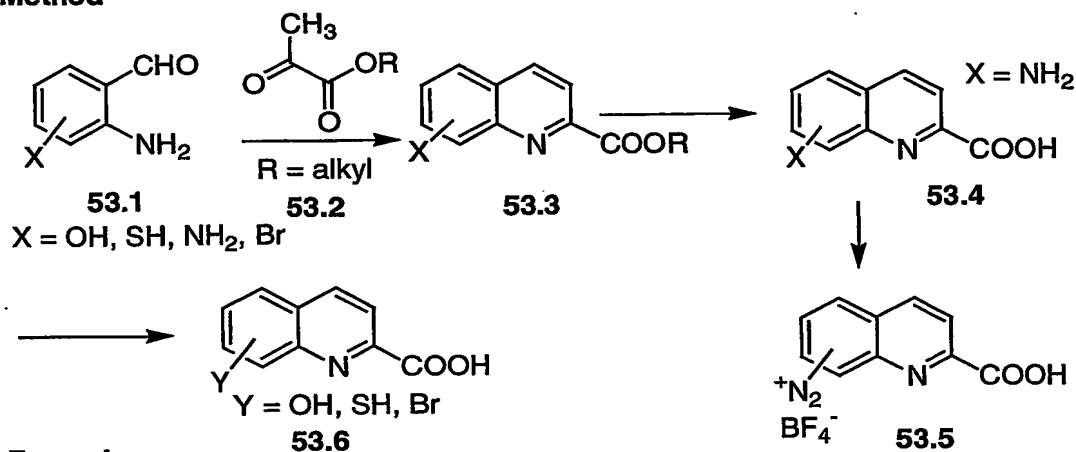
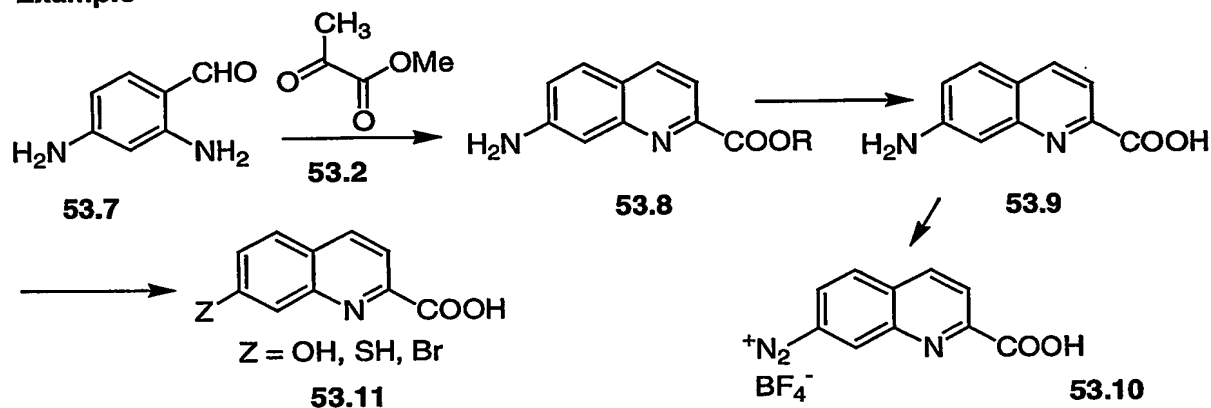
Method



Example



Scheme 51**Method****Example****Scheme 52****Method****Example**

Scheme 53**Method****Example**

Scheme 54 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **54.1** is transformed, via a diazotization procedure as described above (Scheme 53) into the corresponding phenol or thiol **54.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **54.3**, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester **54.4**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products **54.5**. Basic

hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **54.6**.

For example, methyl 6-amino-2-quinoline carboxylate **54.7**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above,
5 into methyl 6-mercaptoquinoline-2-carboxylate **54.8**. This material is reacted with a dialkyl hydroxymethylphosphonate **54.9** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **54.10**. Basic hydrolysis then afford the carboxylic acid **54.11**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline
10 carboxylate **54.7**, different aminoquinoline carboxylic esters **54.1**, and/or different dialkyl hydroxymethylphosphonates **54.3** the corresponding phosphonate ester products **54.6** are obtained.

Scheme **55** illustrates the preparation of quinoline-2-carboxylic acids incorporating
15 phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **55.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **55.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,
20 p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **55.1** and the olefin **55.2** affords the olefinic
25 ester **55.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **55.4**. Optionally, the unsaturated carboxylic acid **55.4** can be reduced to afford the saturated analog **55.5**. The reduction reaction can be effected chemically, for example by the use of diimide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5.
30 For example, methyl 7-bromoquinoline-2-carboxylate, **55.6**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate **55.7** (Aldrich) in the presence of 2 mol% of

tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **55.8**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **55.9**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **55.10**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **55.6**, different bromoquinoline carboxylic esters **55.1**, and/or different dialkyl alkenylphosphonates **55.2**, the corresponding phosphonate ester products **55.4** and **55.5** are obtained.

Scheme **56** depicts the preparation of quinoline-2-carboxylic acids **56.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **56.1** is reacted with a phosphonate aldehyde **56.2** under reductive amination conditions, to afford the aminoalkyl product **56.3**.

The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **56.4** is then hydrolyzed to yield the free carboxylic acid **56.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **56.6**, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **56.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **56.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **56.9**.

Using the above procedures, but employing, in place of the formylmethyl phosphonate **56.2**, different formylalkyl phosphonates, and/or different aminoquinolines **56.1**, the corresponding products **56.5** are obtained.

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 56 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-7, or to precursors thereto, may be changed using established chemical transformations. The interconversions
5 reactions of phosphonates are illustrated in Scheme 57. The group R in Scheme 57 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-7 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-7. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation
10 and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 57.1 into the corresponding phosphonate monoester 57.2 (Scheme 57, Reaction 1) can be accomplished by a number of methods. For example, the ester 57.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester
15 compound 57.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 57.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 57.2 can be effected by treatment of the ester 57.1 with a base such as aqueous
20 sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 57.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 57.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester
25 57.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 57.1 or a phosphonate monoester 57.2 into the
30 corresponding phosphonic acid 57.3 (Scheme 57, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **57.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **57.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **57.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **57.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

- 10 Palladium catalyzed hydrogenolysis of phosphonate esters **57.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **57.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

- The conversion of a phosphonate monoester **57.2** into a phosphonate diester **57.1** (Scheme 57, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **57.2** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl-
20 yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **57.2** to the diester **57.1** can be effected by the use of the Mitsunobu reaction, as described above
25 (Scheme 54). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **57.2** can be transformed into the phosphonate diester **57.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide
30 R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **57.2** is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **57.1**.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 57, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ **57.3** can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1** (Scheme 57, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **57.1**.

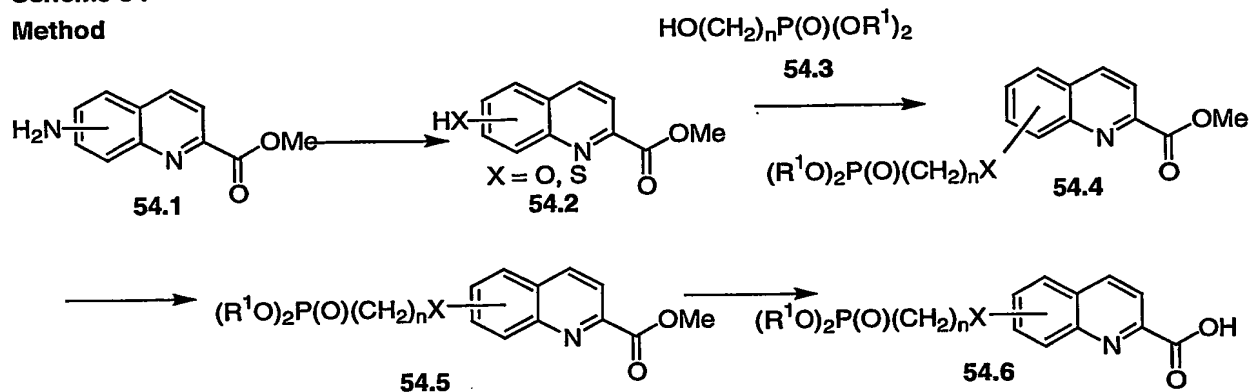
General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes 21 - 56) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into carbinols (Schemes 21 - 26) are applicable to the introduction of phosphonate moieties into the oxirane, thiophenol, aldehyde and quinoline substrates, and the methods described herein for the introduction of phosphonate moieties into the oxirane,

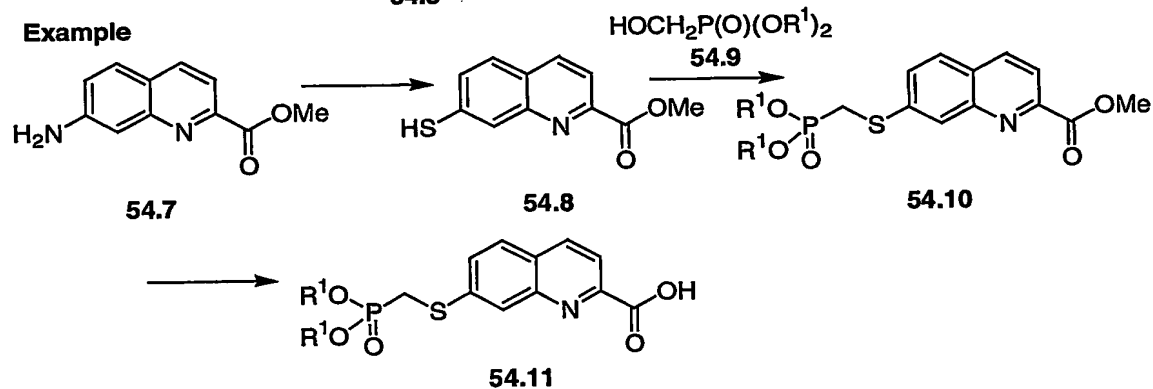
thiophenol, aldehyde and quinoline substrates, (Schemes 27 - 56) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Scheme 54

Method

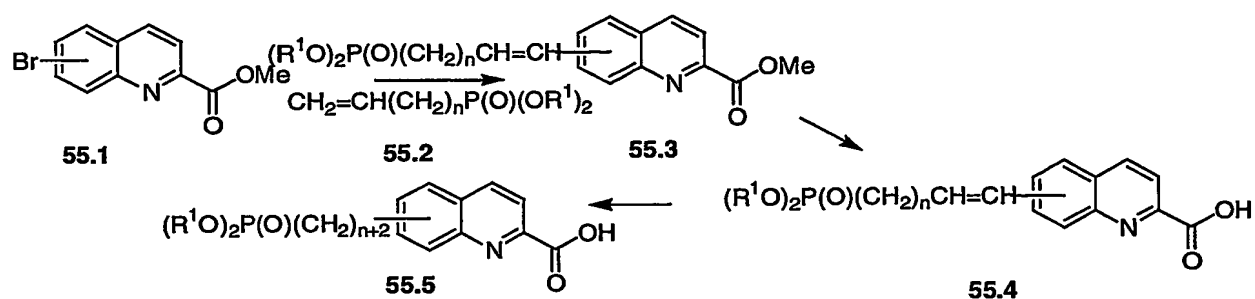


Example

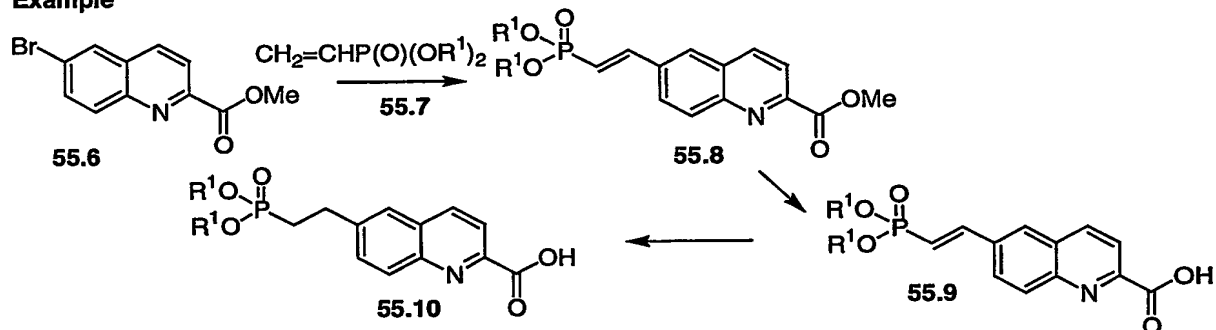


Scheme 55

Method

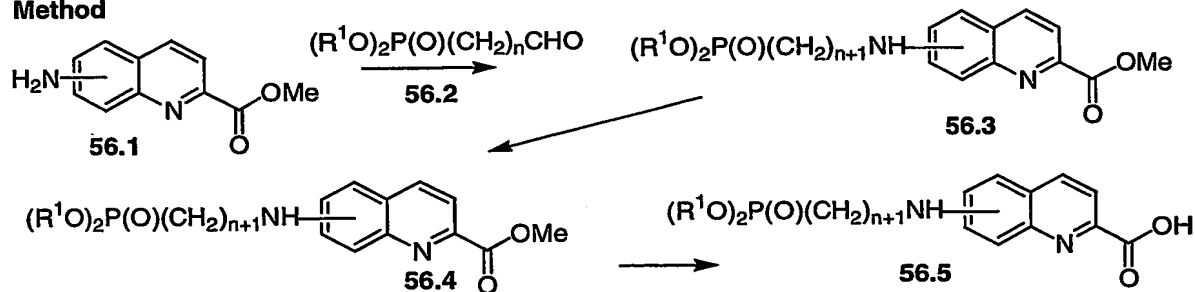


Example

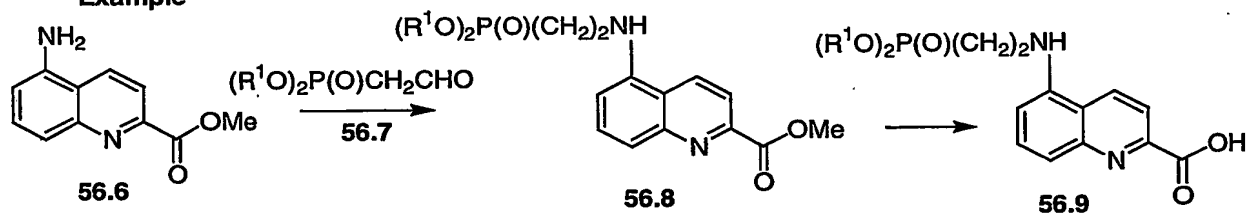


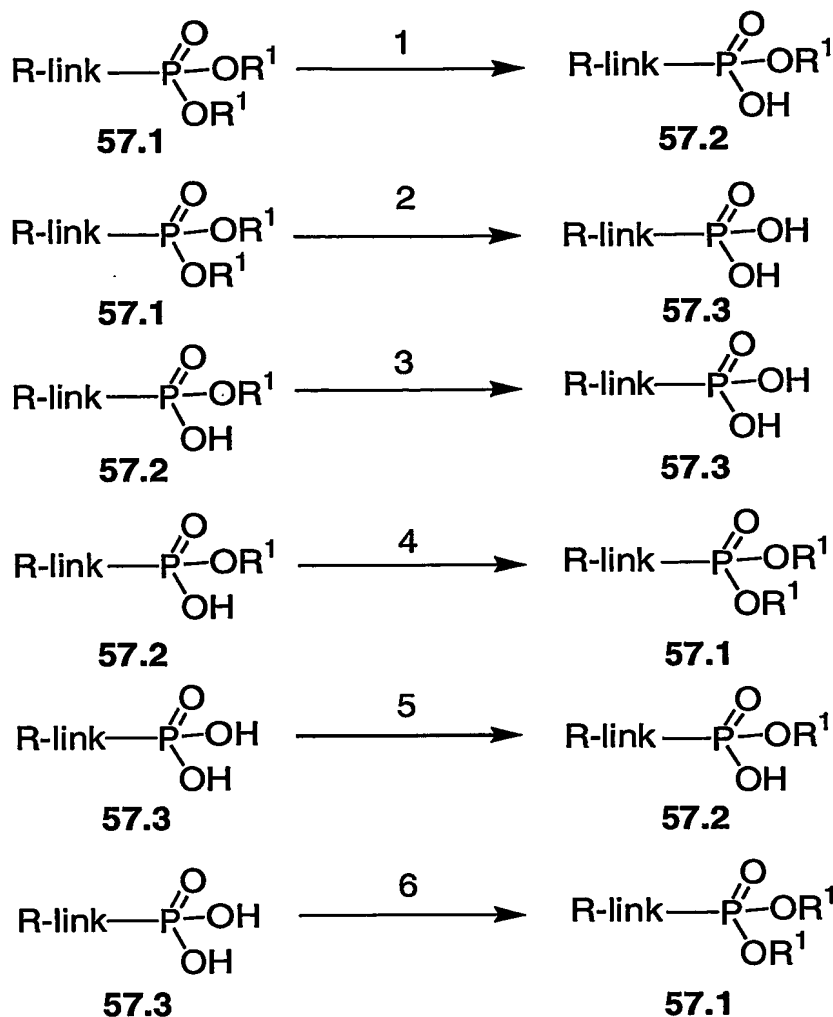
Scheme 56

Method



Example



Scheme 57

Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R²COOH and R⁵COOH.

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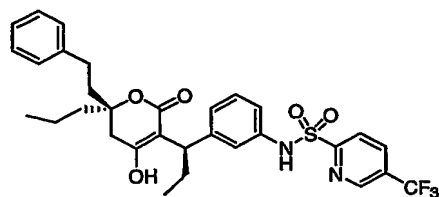
The chemical transformations described in Schemes 1 - 56 illustrate the preparation of compounds 1-5 in which the phosphonate ester moiety is attached to the carbinol moiety, (Schemes 21 - 26), the oxirane moiety (Schemes 27 - 29), the thiophenol moiety (Schemes 30 - 39), the aldehyde moiety (Schemes 40 - 52) or the quinoline moiety (Schemes 53 - 56). The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R²COOH and R⁵COOH, as defined in Charts

10

2a, 2b and 2c. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{5a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 6 and 7. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{5a}COOH$ are the same as those described above (Schemes 1, 5, 7 and 10) for the introduction of the R^2CO and R^5CO moieties.

Tipranavir-like phosphonate protease inhibitors (TLPPD)

Chart 1 illustrates the target compounds of the invention. A linkage group (link) is a portion of the structure that links two substructures, one of which is the scaffold having the structures shown above, the other a phosphonate moiety bearing the appropriate R and R^0 groups, as defined below. The link has at least one uninterrupted chain of atoms, other than hydrogen, typically ranging in up to 25 atoms, more preferably less than 10 atoms (hydrogen excluded). The link can be formed using a variety of functional groups such as heteroatom, carbon, alkenyl, aryl etc. Chart 2 illustrates the intermediate phosphonate compounds of this invention that are used in the preparation of the targets, Chart 1. Chart 3 shows some examples illustrated below of linking groups present in the structures in Chart 1 and 2. The R and R^0 groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for an oxygen linked aryl, alkyl, aralkyl group etc. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group etc and the other a lactate ester.



Tipranavir
US 5852195

Chart 1

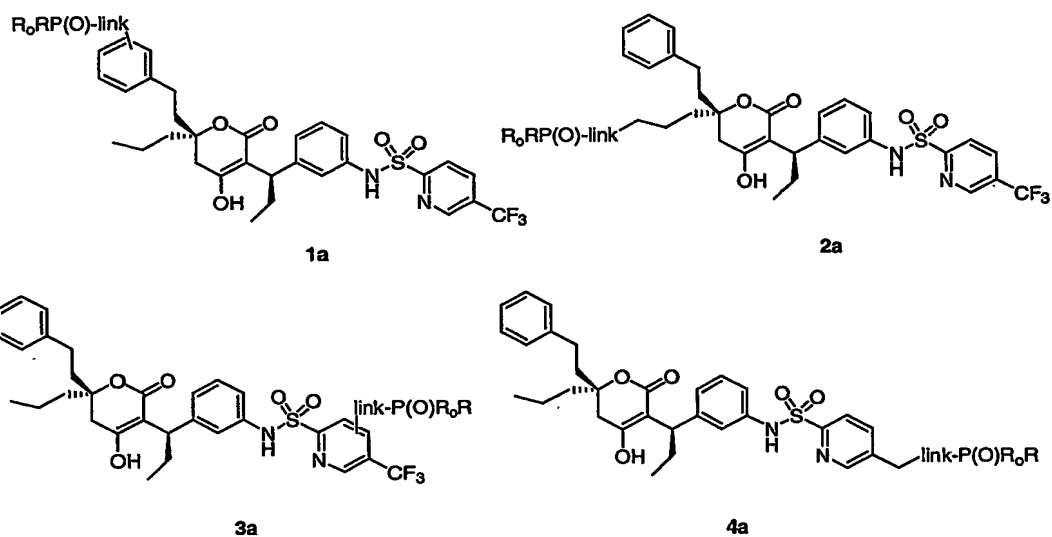
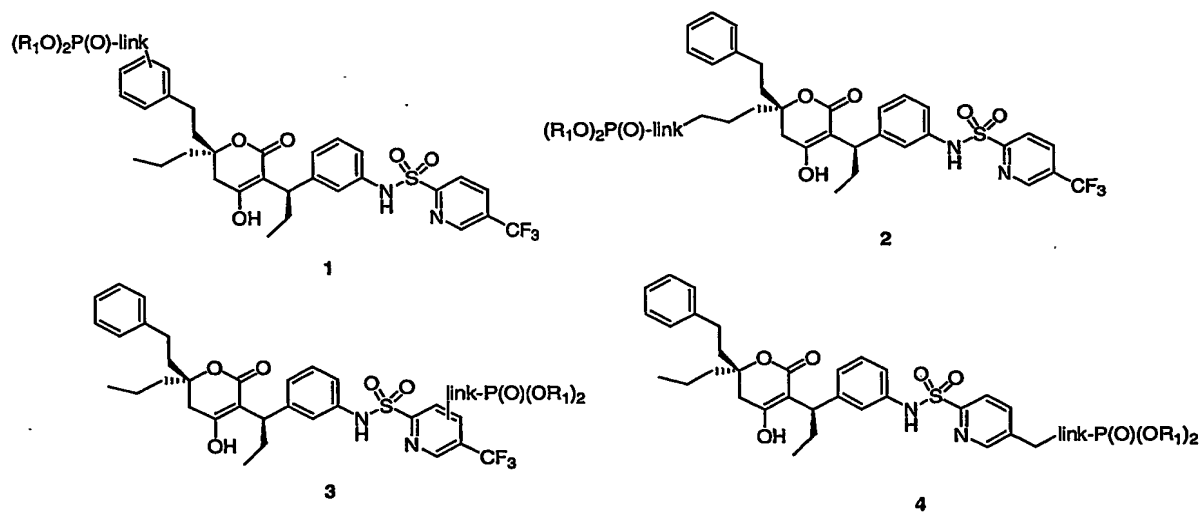
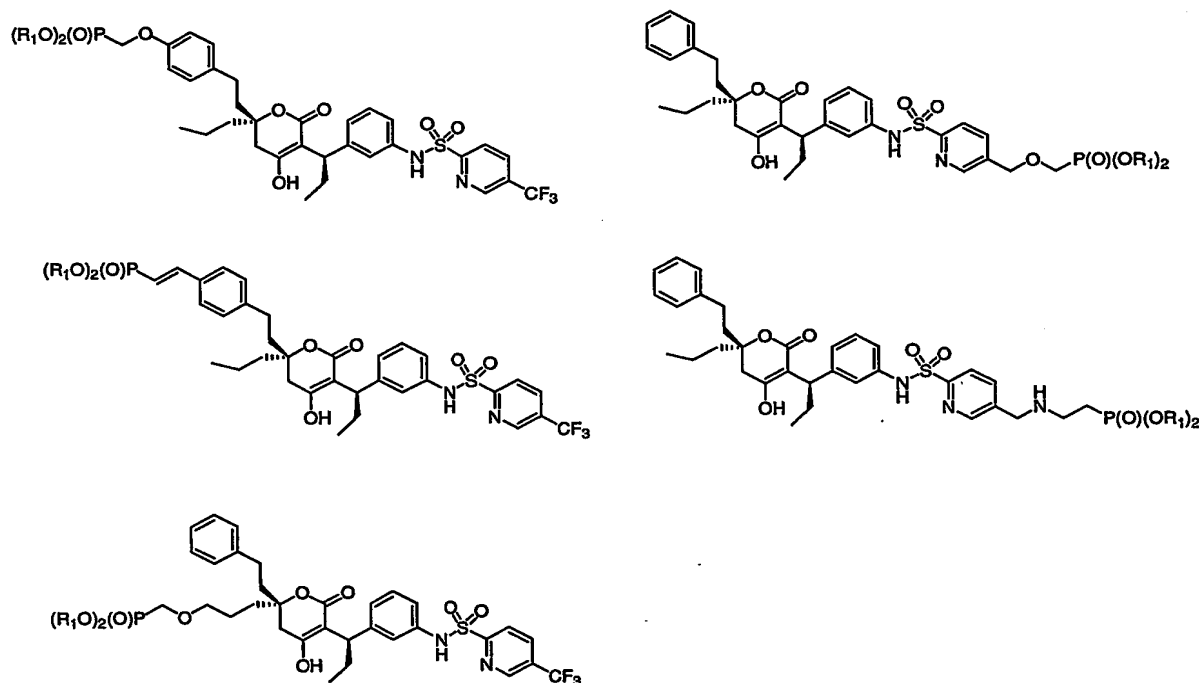


Chart 2



$R_1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

Chart 3



Phosphonate Interconversions

The final compounds described above are synthesized according to the methods described in the following Schemes 1-16. The intermediate phosphonate esters are shown in Chart 2 and these compounds can be used to prepare the final compounds illustrated above in Chart 1, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described in Scheme 16 below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link- $P(O)(OR^1)_2$, where R^1 is defined in Chart 2, or indeed the final stage of $P(O)RR^o$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the

substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-P(O)(OR¹)₂ or P(O)RR^o

In the succeeding examples, the nature of the phosphonate ester group P(O)(OR¹)₂ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 16). Examples shown in charts 1-3 indicate a specific stereochemistry. However, the methods are applicable to the synthesis all of the possible stereoisomers and the separation of possible isomers can be effected at any stage of the sequence after introduction of the stereocenter. The point in the synthetic sequence would be determined by the resolution that could be achieved in the separation by one skilled in the art.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of Intermediate Phosphonates shown in Chart 2

Scheme 1-3 illustrates the synthesis of target molecules of type 1, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The procedures described in J. Med. Chem. 1998, 41, p3467 are used to generate compounds of the type 1 from 1.2 in which A is Hydrogen. The conversion of 1.1 into 1.2 follows procedures described in Bioorg Med. Chem 1999, 7, p2775 for the preparation of a similar compound. The preparation of 1.1 is described in Scheme 13-14. For example, acid 1.1 is converted via the Weinreb amide to the ketone 1.2. The ketone 1.2 is then treated with 3-oxo-butyric acid methyl ester, as described in J. Med Chem. 1998, 41, 3467, to give the pyrone 1.3. A mixture of R and S isomers can be carried forward or alternatively separated by chiral chromatography at this stage. Aluminium chloride catalysed condensation of 3-nitrobenzaldehyde onto the pyrone 1.3, as described in J. Med

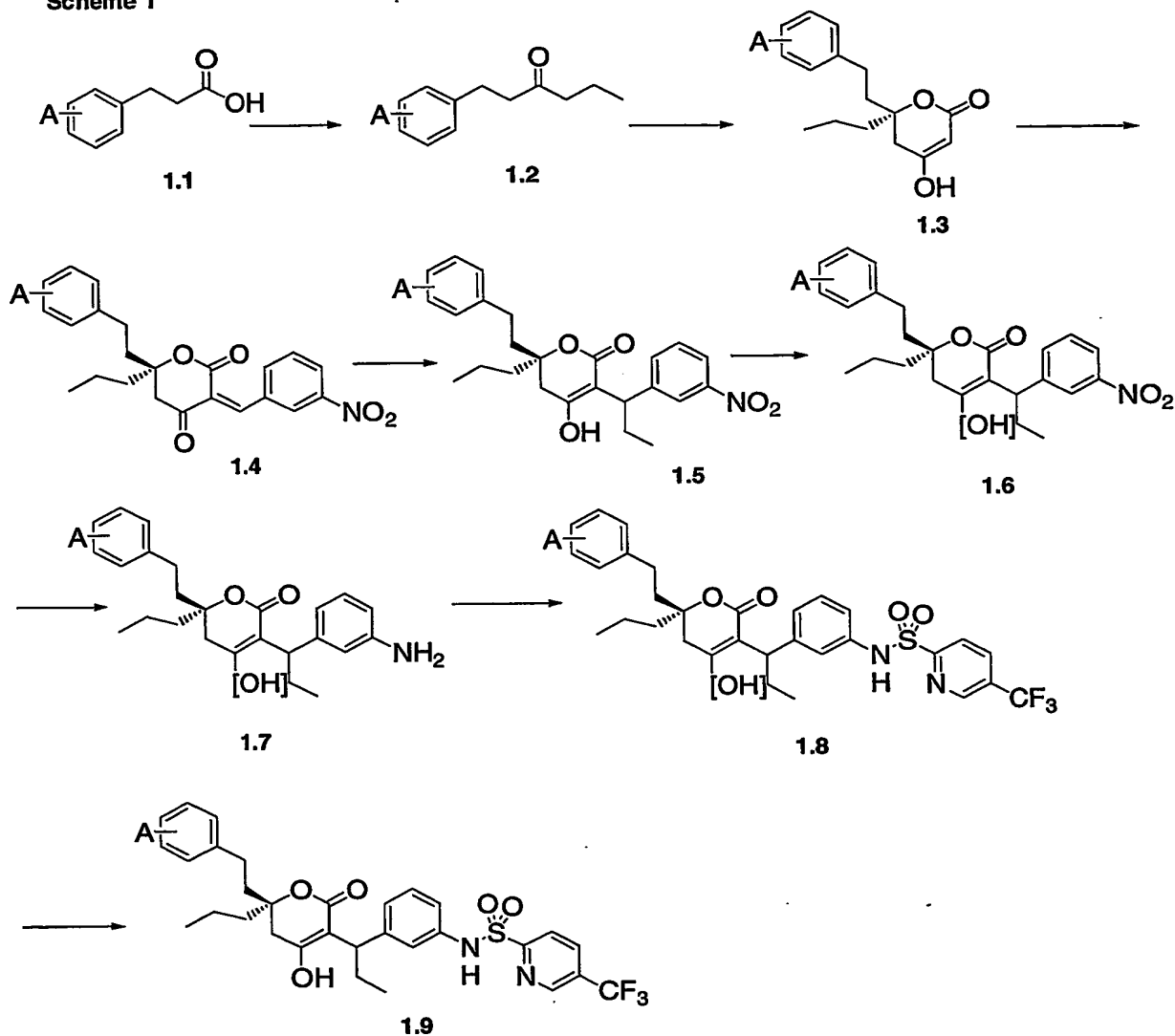
Chem. 1998, 41, 3467-3476, affords nitro pyrone **1.4**. Nitro pyrone **1.4** upon treatment with triethylaluminum in the presence of copper(1) bromide-dimethylsulfide as described in J. Med Chem. 1998, 41, 3467-3476 affords the dihydropyrone **1.5**. Protection of the dihydropyran hydroxyl in **1.5** with a suitable protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff gives the hydroxyl protected compound **1.6**. For example, treatment with SEMCl in the presence of base e.g. potassium carbonate, generates the SEM ether protected **1.6**. Catalytic hydrogenolysis of the nitro group, as described in J. Med Chem. 1998, 41, 3467-3476, affords the aryl amine **1.7** which is then coupled with the 5-trifluoromethyl-pyridine-2-sulfonyl chloride in the presence of pyridine, as described in J. Med Chem. 1998, 41, 3467-3476 to afford the sulfonamide **1.8**. Finally, removal of the protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff affords the product **1.9**. For example, treatment of the SEM protected product indicated above with TBAF produces the de-silylated (6R, 3R/S) product **1.9**. The diastereoisomers are then separated through silica gel chromatography.

Scheme 2 also illustrates the synthesis of target molecules of type **1**, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂ but the products in this example have the absolute stereochemistry (6R, 3R). The ketone **1.2**, prepared in Scheme 1, is transformed into the dihydropyrone **2.2** as described in Drugs of the Future, 1998, 23(2), p146. This 2 step reaction involves reaction of the ketone with dioxalone **2.1**, prepared as described in Drugs of the Future, 1998, 23(2), p146 in the presence of Ti(OBu)Cl₃, followed by treatment with a base such as potassium tert-butoxide. Treatment of the dihydropyrone **2.2** with the same procedures reported in Scheme 1 for the conversion of **1.5** into **1.9** then affords the final product **1.9** in chiral form (6R, 3R). For example, the pyrone hydroxyl **2.2** is first protected as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff, to afford **2.3** and then the dibenzyl groups are removed from **2.3** by catalytic hydrogenolysis as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.579 to afford the amine product **1.7**. Amine **1.7** is then converted into **1.9** as described in Scheme 1.

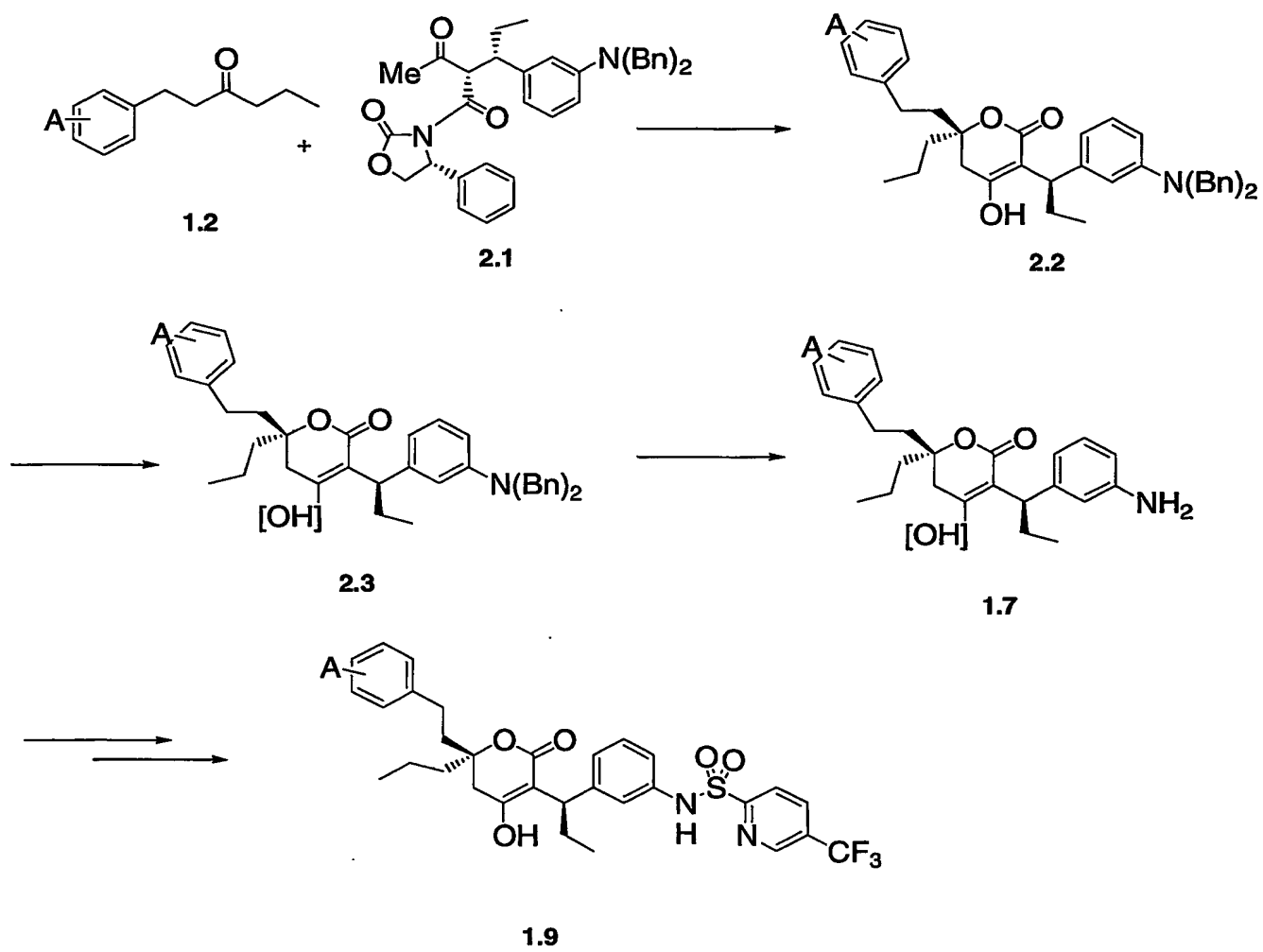
The reactions shown in Scheme 1-2 illustrate the preparation of the compounds **1.9** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 3 depicts the conversion of the compounds **1.9** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **1**. In this procedure, the compounds **1.9** are

5 converted, using the procedures described below, Schemes 10-15, into the compounds **1**.

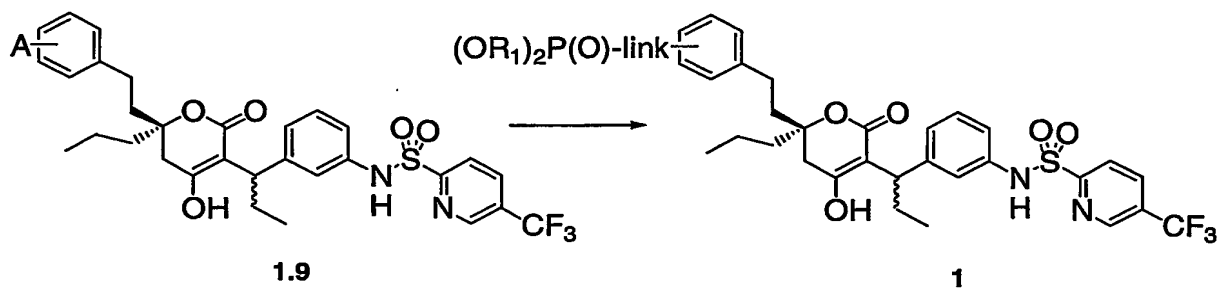
Scheme 1



Scheme 2



Scheme 3

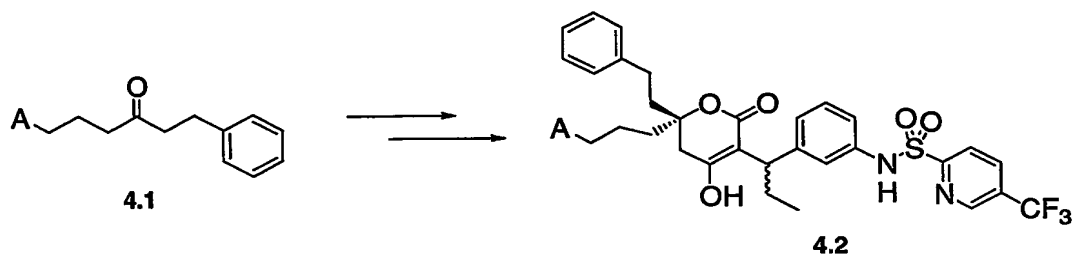


Scheme 4 illustrates the synthesis of target molecules of type 2, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The acid 4.1 prepared as described below (Scheme 15), is converted into 4.2 using the procedures described in Scheme 1 or Scheme 2.

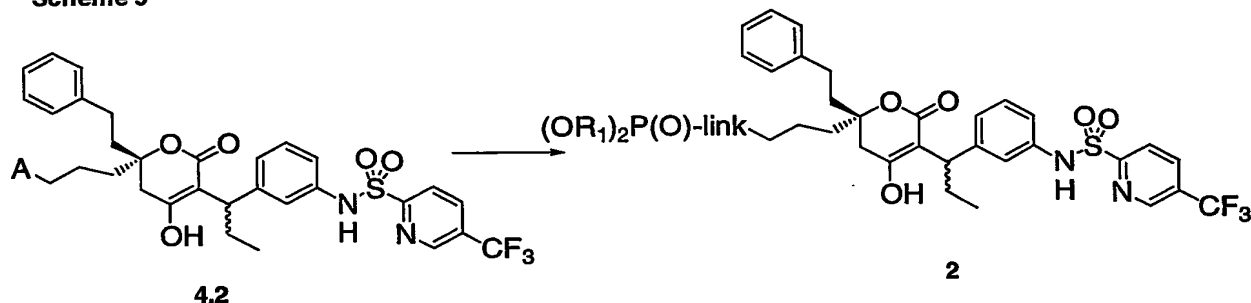
- 5 The reactions shown in Scheme 4 illustrate the preparation of the compounds 4.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 5 depicts the conversion of the compounds 4.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2. In this procedure, the compounds 4.2 are converted, using the procedures described below, Schemes 10-15, into the compounds 2.

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Scheme 4



Scheme 5

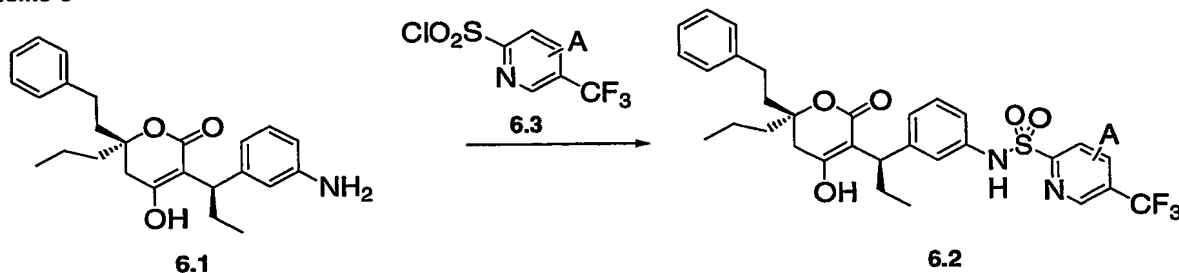


- 15 Scheme 6-7 illustrates the synthesis of target molecules of type 3, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The amine 6.1 prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide 6.2 using the procedures described in Scheme 1 or Scheme 2 for the preparation of 1.8 from 1.7. The synthesis of the sulfonyl chlorides 6.3 is shown below in Schemes 11-12.

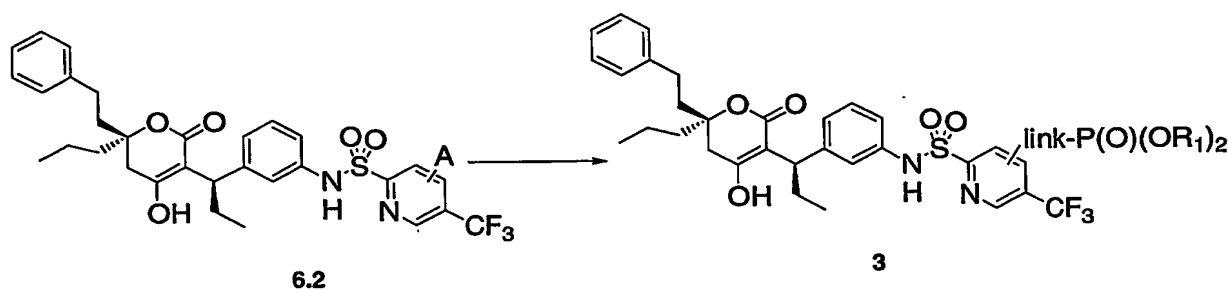
- 20 The reactions shown in Scheme 6 illustrate the preparation of the compounds 6.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 7 depicts the conversion of the compounds 6.2 in which A is [OH], [SH], [NH],

Br etc, into the phosphonate esters **3**. In this procedure, the compounds **6.2** are converted, using the procedures described below, Schemes **10-15**, into the compounds **3**.

Scheme 6



Scheme 7



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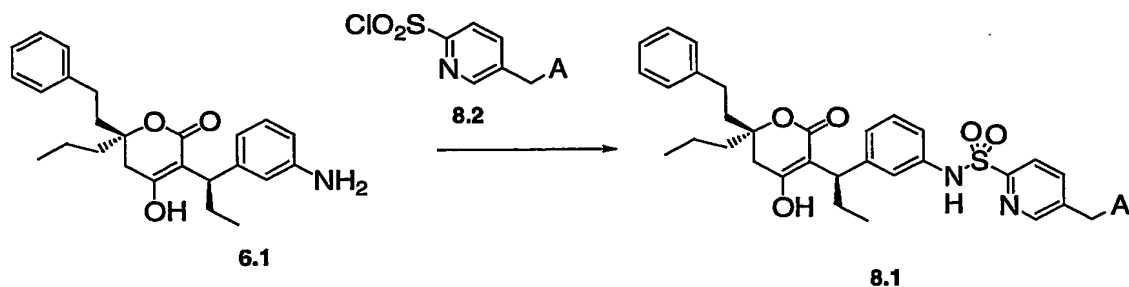
Scheme **8** illustrates the synthesis of target molecules of type **4**, chart 2, in which A is Br, Cl, [OH], [NH], or the group $\text{link-P(O)(OR}^1)_2$. The amine **6.1** prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide **8.1** by treatment with **8.2** using the procedures described in Scheme 1 or Scheme 2. The synthesis of the sulfonyl chlorides **8.2** is shown below in Scheme **10**.

10

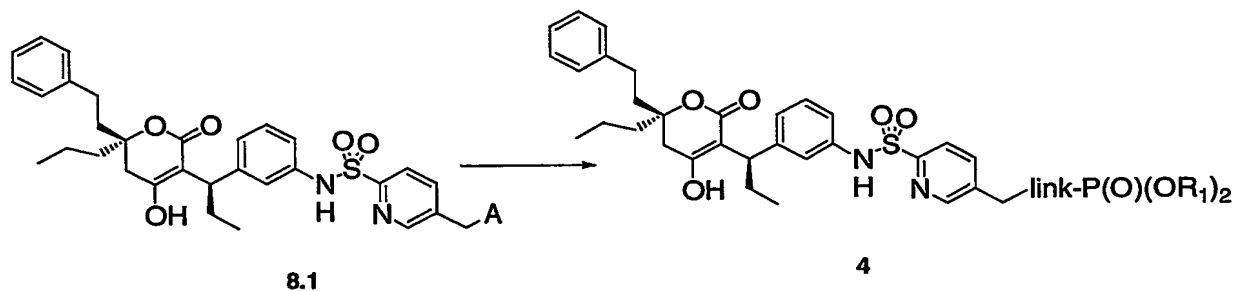
The reactions shown in Scheme **8** illustrate the preparation of the compounds **8.1** in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **9** depicts the conversion of the compounds **8.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4**. In this procedure, the compounds **8.1** are converted, using the procedures described below, Schemes **10-15**, into the compounds **4**.

15

Scheme 8



Scheme 9



Preparation of phosphonate reagents used in the synthesis of compounds 1-4

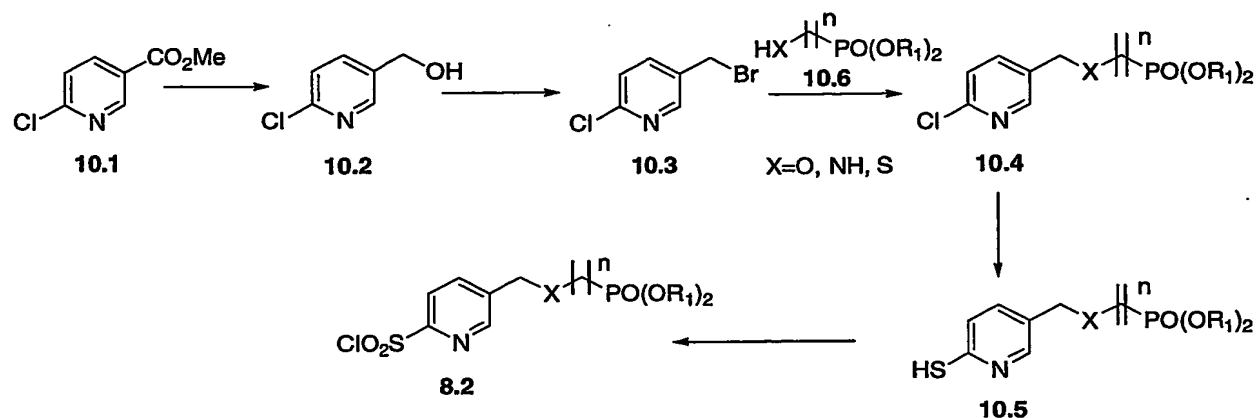
- 5 Schemes 10 describes the preparation of phosphonate-containing derivatives 8.2, in which the phosphonate is linked through a heteroatom, which are employed in the preparation of the phosphonate ester intermediates 4. The pyridyl ester 10.1 (Acros) is first reduced to the alcohol 10.2. This transformation involves reducing the ester with lithium aluminium hydride, or other reducing agent, in an inert solvent such as THF or dioxane. Alcohol 10.2 is then
- 10 converted to the bromide 10.3 through typical hydroxyl to bromide conversion conditions described in Comprehensive Organic Transformations, R.C. Larock, 2nd edition, p693-697. For instance, treatment of 10.2 with carbon tetrabromide and triphenylphosphine in THF or dioxane affords the bromide 10.3. Treatment of the bromide 10.3 with a thiol, amino, or hydroxyl alkyl phosphonate 10.6 then affords the phosphonate product 10.4. The reaction is
- 15 performed in the presence of a base, in a polar aprotic solvent such as dioxane or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 10.6. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. The chloride 10.4 is then treated KHS in
- 20 methanol, as described in Justus Liebigs Annalen Chemie, 1931, p105 or thiourea followed by

potassium hydroxide treatment, as described in Heterocycles 1984, p117, to give the α -sulfide **10.5**. If appropriate, reactive groups e.g. amines in the phosphonate chain, are protected using methods known to one skilled in the art. The α -sulfide **10.5** is then converted to the sulfonyl chloride **8.2** by treatment with chlorine in HCl, as described in Synthesis 1987, 4, p409, or J. Med. Chem 1980,12, p1376.

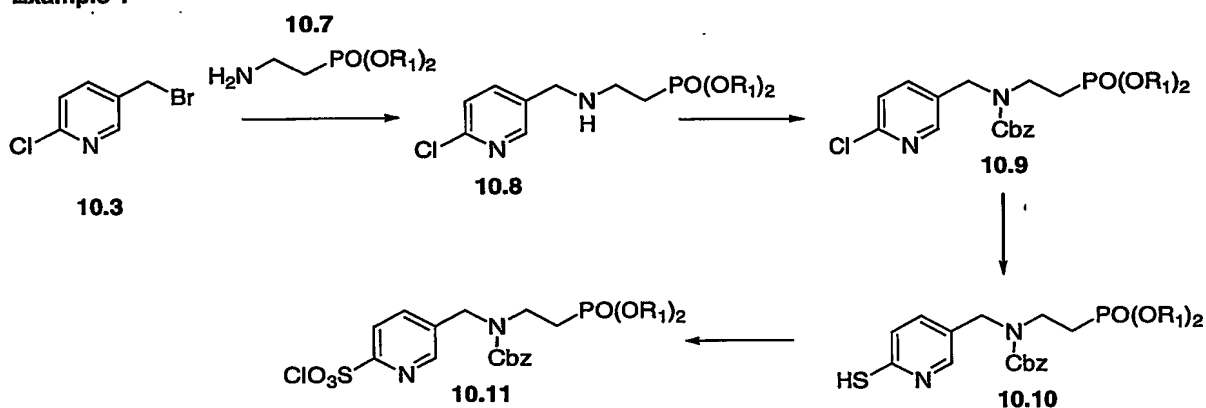
For example, the pyridyl bromide **10.3**, described above, is treated with amino phosphonate **10.7**, prepared as described in J. Org. Chem. 2000, 65, p676, in the presence of potassium carbonate and DMF to afford the phosphonate product **10.8**. Protection of the amine by conversion to the CBZ carbamate **10.9** is performed by treatment of **10.8** with benzyl chloroformate in the presence of triethylamine. Further treatment of **10.9** with thiourea in ethanol at reflux followed by treatment with potassium hydroxide in water then affords the thiol **10.10**. Thiol **10.10** is then treated with chlorine in HCl (aqueous) to afford the sulfonyl chloride **10.11**. Using the above procedures, but employing, in place of the amino alkyl phosphonate **10.7**, different alkyl phosphonates **10.6**, the corresponding products **8.2** are obtained.

Alternatively (Example 2), illustrates the preparation of phosphonates in which the link is through an oxygen atom. The pyridyl bromide **10.3** described above, is treated with hydroxyl phosphonate **10.12**, prepared as described in Synthesis 1998, 4, p327, in the presence of potassium carbonate and DMF to afford the phosphonate product **10.13**. Further treatment of **10.13**, as described above, for the conversion of **10.8** into **10.11** affords the sulfonyl chloride **10.16**. Using the above procedures, but employing, in place of the hydroxy alkyl phosphonate **10.12**, different alkyl phosphonates **10.6** the corresponding products **8.2** are obtained.

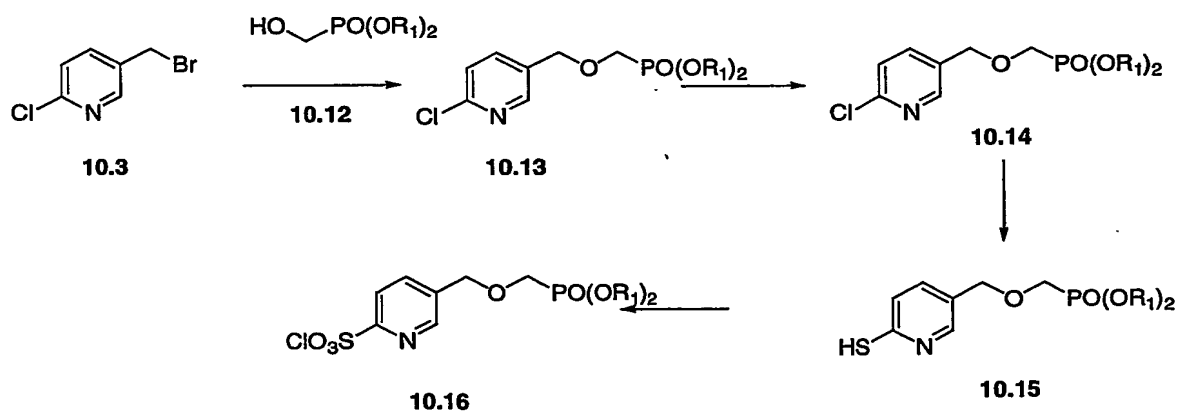
Scheme 10



Example 1



Example 2



5 Schemes 11-12 describe the preparation of phosphonate-containing derivatives **6.3**, which are employed in the preparation of the phosphonate ester intermediates **3**. Scheme 11 illustrates compounds of type **6.3** in which the link is through a oxygen, sulfur or nitrogen heteroatom.

Pyridyl halide **11.1** is treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate **10.6** to give the product **11.3**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong
5 base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Upon formation of **11.3** the pyridine is converted to the α -chloro pyridine **11.4** by treatment with chlorine at high temperature in a sealed vessel as described in Recl. Trav. Chim Pays-Bas 1939, 58, p709 or, preferably, the α -chloro compound is generated by treatment of
10 **11.3** with butyl lithium in hexane and $\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$ followed by addition of a chloride source such as hexachloroethane, as described in Chem Commun. 2000, 11, p951. Chloride **11.4** is then converted to the thiol **11.4** as described above (Scheme 10). Thiol **11.5** is then converted to the sulfonyl chloride **6.3** as described in Scheme 10.

15 For example, bromo pyridine (Apollo) **11.6** is treated with amine **10.7** in the presence of cesium carbonate in THF or alternative solvent at reflux to give the amine **11.7**. The amine is then converted to the sulfonyl chloride **11.9** through the intermediate chloride **11.8** as described in Scheme 10. Using the above procedures, but employing, in place of the amino alkyl phosphonate **10.7**, different alkyl phosphonates **10.6**, and in place of the pyridine **11.6**
20 different halo pyridines **11.1**, the corresponding products **6.3** are obtained.

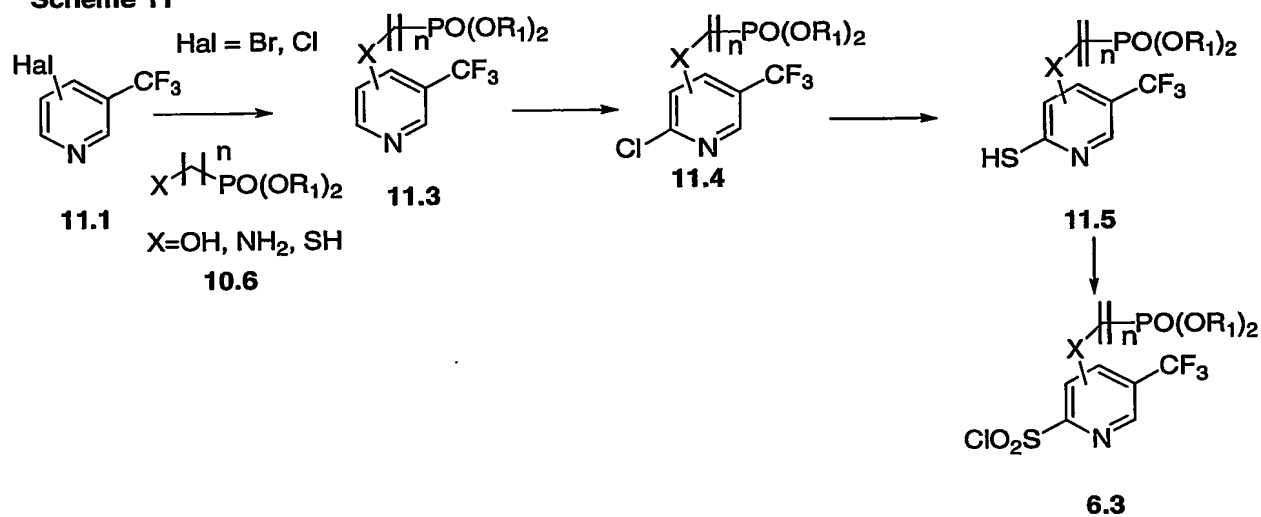
Alternatively the bromo pyridine **11.6** (Apollo) is treated with thiol **11.10**, prepared as described in Zh. Obschei. Khim 1973, 43. p2364, in the presence of cesium carbonate in THF or alternative solvent at reflux to give the thiol **11.11**. The thiol is then converted to the
25 sulfonyl chloride **11.12** as described above for the conversion of **11.7** into **11.9**. Using the above procedures, but employing, in place of the thiol alkyl phosphonate **11.10**, different alkyl phosphonates **10.6**, and in place of the pyridine **11.6** different halo pyridines **11.1**, the corresponding products **6.3** are obtained.

30 Scheme 12 illustrates compounds of type **6.3** in which the phosphonate is attached through an unsaturated or saturated carbon linker. In this procedure, pyridyl bromo compound **11.1** is treated under a palladium catalyzed Heck coupling conditions with the alkene **12.1** to give the

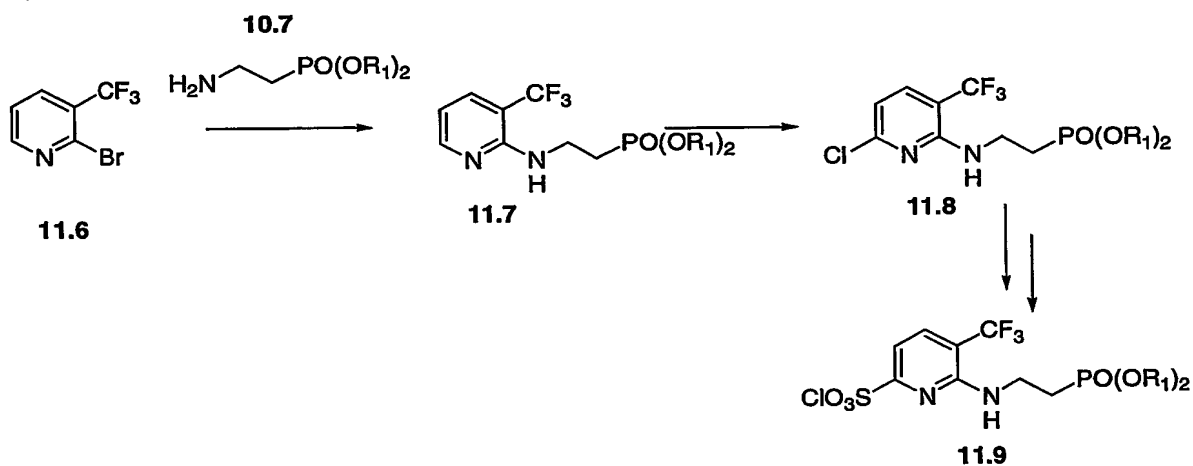
coupled alkene **12.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **12.2**. Optionally, the product **12.2** can be reduced to afford the saturated phosphonate **12.4**. Methods for the reduction of carbon-carbon double bonds are described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide. Following the Heck reaction or reduction the pyridyl compounds **12.2** and **12.4** are converted to the sulfonyl chlorides **12.3** and **12.5** respectively, using the same procedures described in Scheme 11 for the conversion of **11.3** into **6.3**

For example, pyridine **11.6** (Aldrich) is reacted with a dialkyl propenyl phosphonate **12.6**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371, to afford the coupled product **12.7**. The product **12.7** is then reduced, for example by reaction with diimide, as described in *J. Org. Chem.*, 30, 3965, 1965, to afford the saturated product **12.9**. Conversion of the products **12.7** and **12.9** into the sulfonyl chlorides **12.8** and **12.10** respectively follows the same procedures described above for the conversion of pyridine **11.7** into **11.9**. Using the above procedures, but employing, in place of the halo pyridine compound **11.6**, different pyridines **11.1**, and/or different phosphonates **12.1** in place of **12.6**, the corresponding products **12.3** and **12.5** are obtained.

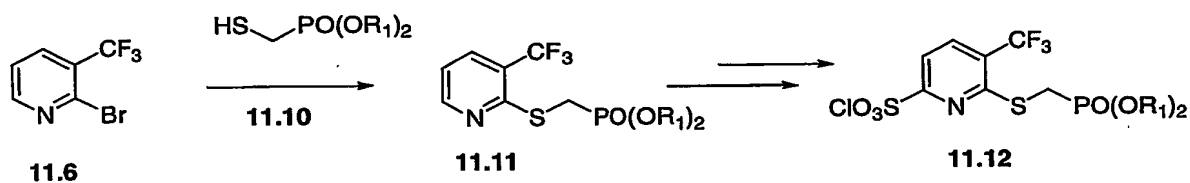
Scheme 11



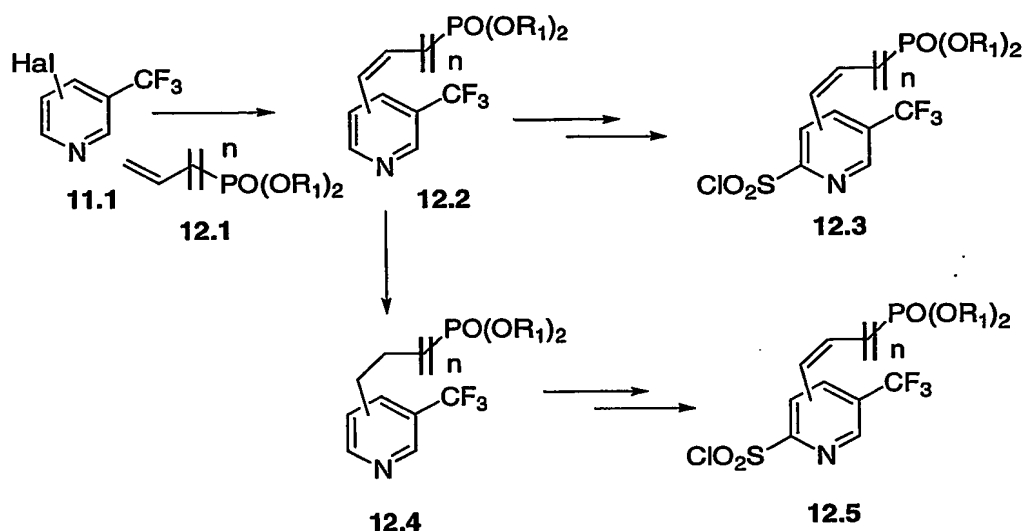
Example 1



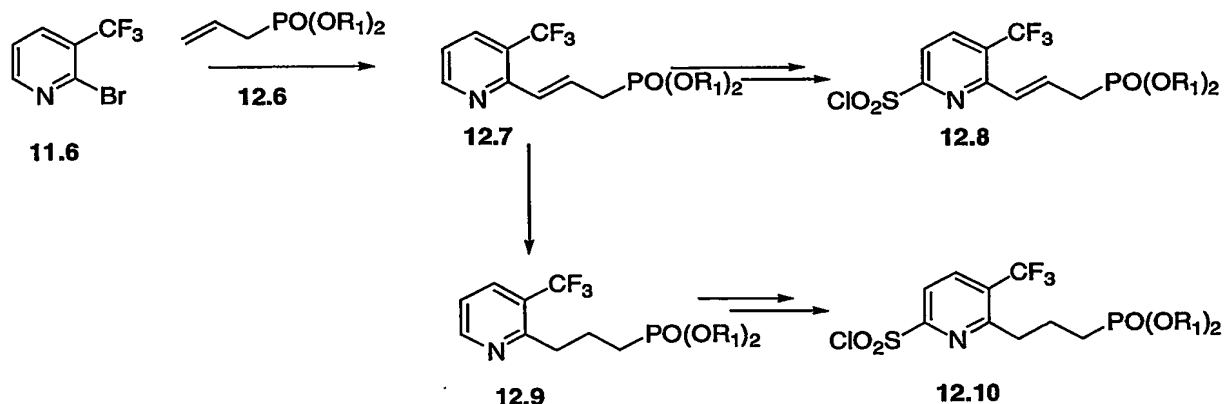
Example 2



Scheme 12



Example 1



- 5 Schemes 13-14 illustrate the preparation of phosphonate containing compounds 1.1 that are used in the preparation of the compounds of type 1, chart 2. Scheme 13 illustrates the preparation of phosphonates 1.1 in which the phosphonate is attached through a heteroatom such as S, O or N. The aryl halide 13.1 bearing a hydroxyl, amino or thiol group, is treated with one equivalent of the phosphonate alkylating agent 13.2, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl etc, in the presence of base e.g. potassium or cesium carbonate in DMF, to give the compound 13.3. The product 13.3 is then converted to the alkene 13.4 using a palladium mediated Heck coupling with Methyl acrylate as described
- 10

above, Scheme 12. The acrylate is reduced as described in Scheme 12 and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

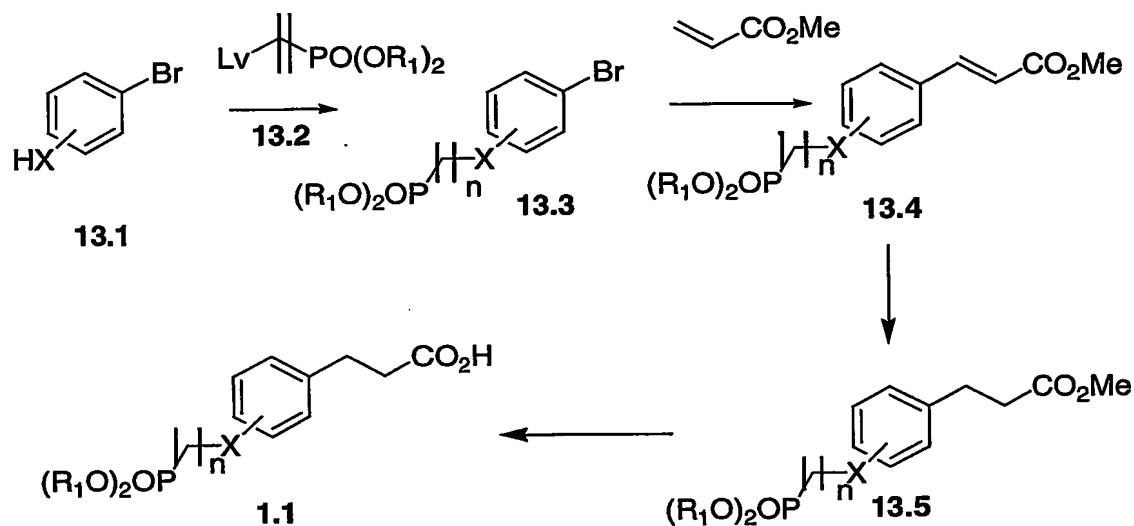
For example, the halide 13.6 (Aldrich) is treated with triflate phosphonate 13.7, prepared as described in Tet. Lett. 1986, 27, p1497, and potassium carbonate in DMF, to give the ether 13.8. The ether is then treated with methyl acrylate under Heck coupling conditions as described in J. Med. Chem. 1992, 35, p1371, to give the alkene 13.9. 13.9 is reduced by treatment with diimide, as described analogously in Bioorg Med. Chem. 1999, 7, p2775 to give the saturated aryl ester 13.10. Treatment of 13.10 with lithium hydroxide in THF and water then affords the acid 13.11. Using the above procedures, but employing, in place of the aryl halide 13.6, different aryl halides 13.1, and/or different phosphonates 13.2 in place of 13.7, the corresponding products 1.1 are obtained.

Scheme 14 illustrates the preparation of phosphonates 1.1 in which the link is through a carbon bond and a nitrogen heteroatom. The aryl halide bearing an carbonyl group is treated with one equivalent of the amino alkyl phosphonate 14.2 under reductive amination conditions to give the amine 14.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 14.3. The amine product 14.3 is then converted to the alkene 14.4 using a palladium mediated Heck coupling with Methyl acrylate as described above, Scheme 13. The acrylate is then reduced as described in Scheme 13 to give 14.5, and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

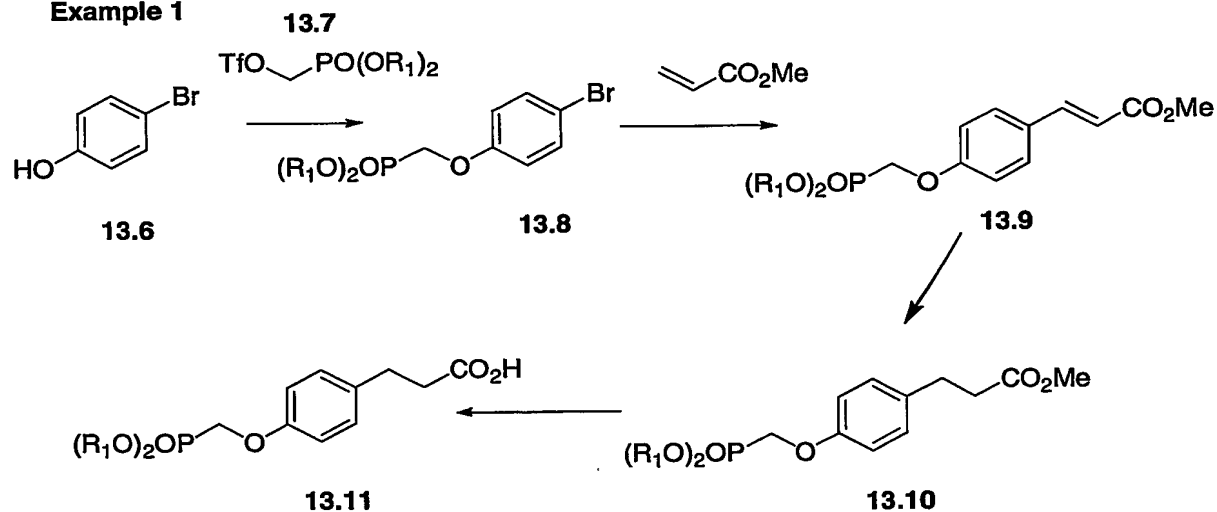
For example, the halide 14.6 (Aldrich) is treated with amino phosphonate 10.7, prepared as described above, in methanol for 30 min. After 30 min sodium borohydride is added to give the amine 14.7. The amine 14.7 is then treated with methyl acrylate under Heck coupling conditions as described above, to give the alkene 14.8. Alkene 14.8 is reduced as described in Scheme 13 to give the saturated ester 14.9. Treatment of 14.9 with lithium hydroxide in THF and water then affords the acid 14.10. Using the above procedures, but employing, in place of

the aryl halide **14.6**, different aryl halides **14.1**, and/or different amino phosphonates **14.2** in place of **10.7**, the corresponding products **1.1** are obtained.

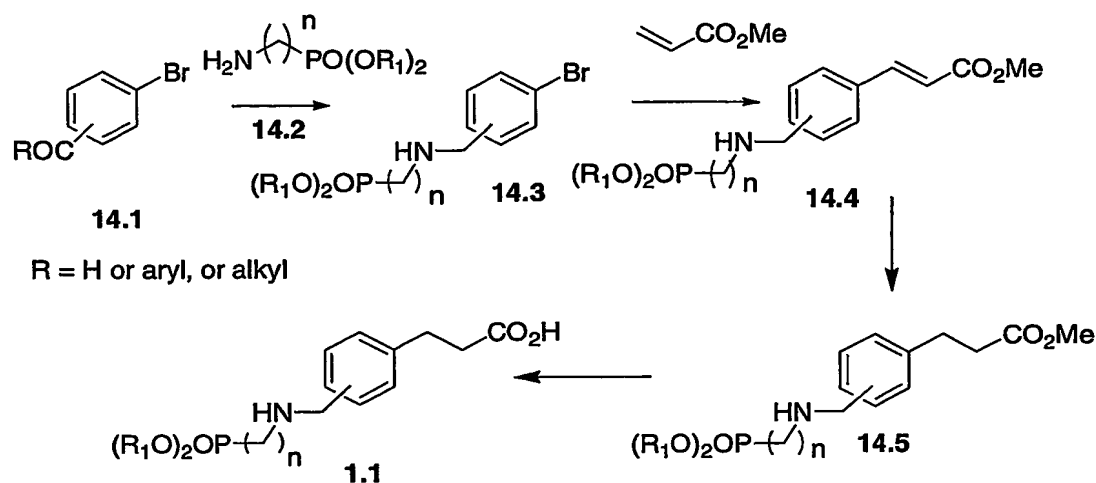
Scheme 13



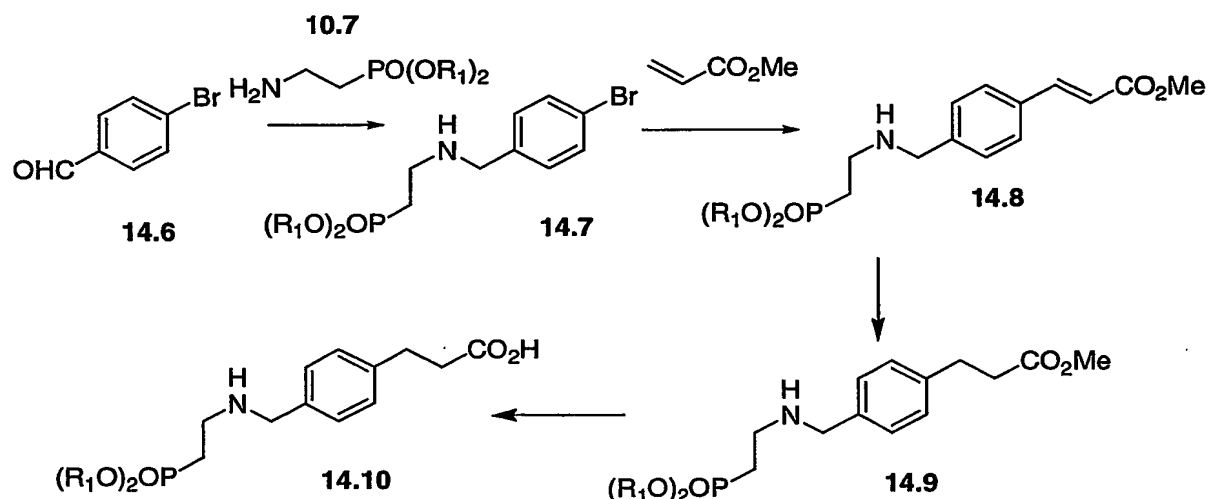
Example 1



Scheme 14



Example 1



- 5 Scheme 15 describes the preparation of phosphonate-containing derivatives 4.1 which are employed in the preparation of the phosphonate ester intermediates 2, chart 2. The alcohol 15.1 prepared as described in J. Org Chem. 1994, 59, p3445, is treated with ethylene glycol and a catalytic amount of tosic acid in benzene at reflux to give the 1,3-dioxalane 15.2. The dioxalane is then treated with carbon tetrabromide and triphenyl phosphine in acetonitrile, or
- 10 alternate conditions as described in Comprehensive Organic Transformations, R.C. Larock, 2nd editions, p693-697, to generate the bromide 15.3. Bromide 15.3 is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate 10.6 to give the product 15.4. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan

or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Following preparation of **15.4** the dioxalone is removed as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.317.

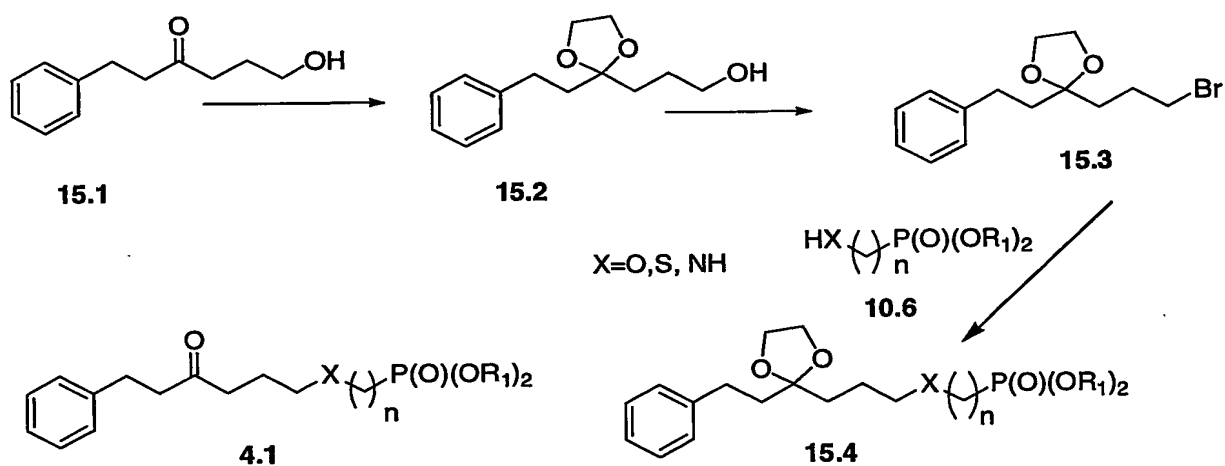
For example, **15.5** described above, is treated with alcohol **10.12**, prepared as described in Scheme 10, in DMF and potassium carbonate at ca 80 °C to give the phosphonate **15.7**.

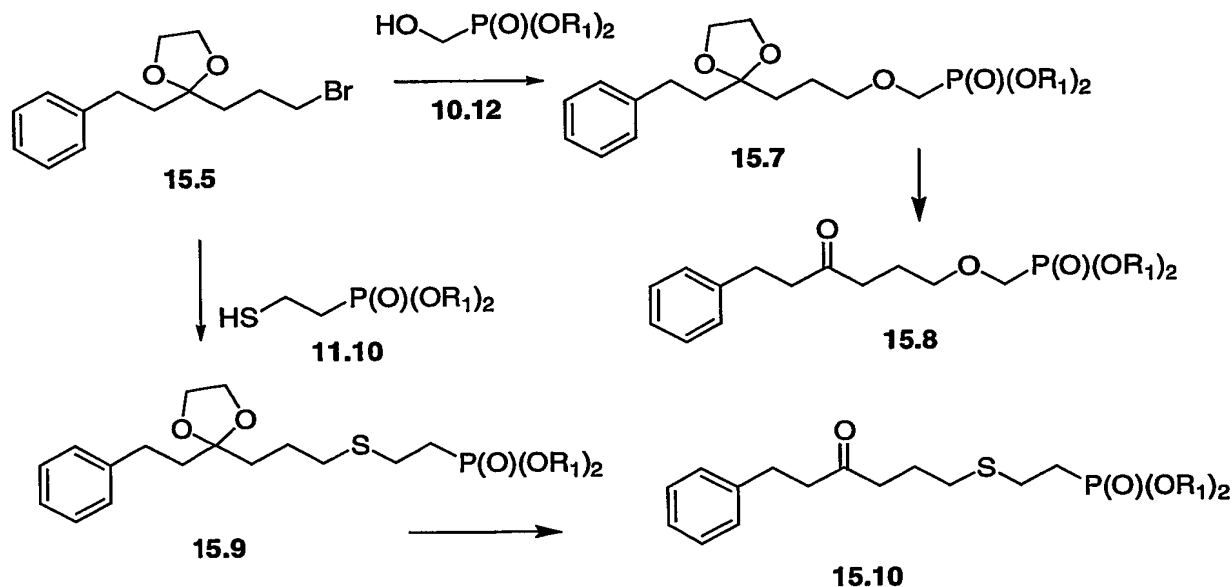
Alternatively bromide **15.5** is then heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **11.10**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **15.9**.

Treatment of **15.7** and **15.9** with aqueous HCl in THF then affords the ketones **15.8** and **15.10** respectively. Using the above procedures, but employing, in place of **10.12** and **11.10**,

different alkyl phosphonates **10.6** the corresponding products, **4.1** are obtained.

Scheme 15



Example 1**General applicability of methods for introduction of phosphonate substituents.**

The procedures described for the introduction of phosphonate moieties (Schemes 10-15) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, for example, the methods described above for the introduction of phosphonate groups onto the pyridyl ring of **11.1**, are also applicable to the introduction of phosphonate moieties onto the aryl rings of **13.1** and **14.1**, and the reverse is also true.

10 Interconversions of the phosphonates between R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

The schemes above describe the preparation of phosphonates of general structure R-link-P(O)(OR¹)₂ in which the R¹ groups are defined as indicated in Chart 2, and the R group refers to the scaffold. The R¹ groups attached to the phosphonate esters in Chart 2 may be changed using established chemical transformations. The interconversion reactions of the phosphonates attached through the link group to the scaffold (R) are illustrated in Scheme 16. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate

transformation depend on the nature of the substituent R^1 . The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

5 The conversion of a phosphonate diester **16.1** into the corresponding phosphonate monoester **16.2** (Scheme 16, Reaction 1) can be accomplished by a number of methods. For example, the ester **16.1** in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound **16.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the
10 diester **16.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **16.2** can be effected by treatment of the ester **16.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **16.2** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **16.2** in which R^1 is alkyl by hydrogenation,
15 for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **16.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl
20 carboxylates.

The conversion of a phosphonate diester **16.1** or a phosphonate monoester **16.2** into the corresponding phosphonic acid **16.3** (Scheme 16, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example,
25 dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **16.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **16.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **16.2** in which R^1 is alkenyl such as,
30 for example, allyl, can be converted into the phosphonic acid **16.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous

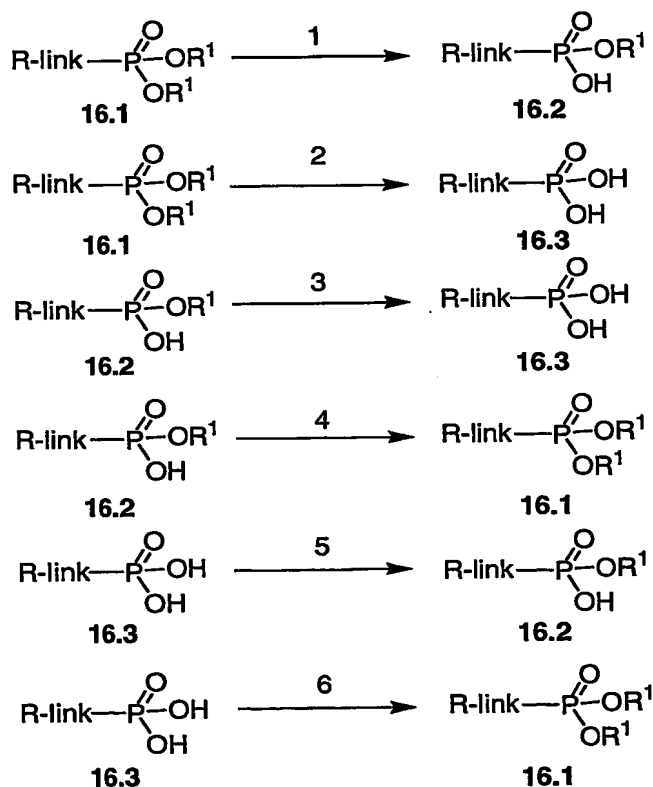
ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

Palladium catalyzed hydrogenolysis of phosphonate esters **16.1** in which R¹ is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **16.1** in which R¹ is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

- 5 The conversion of a phosphonate monoester **16.2** into a phosphonate diester **16.1** (Scheme 16, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **16.2** is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a
- 10 carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
- 15 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine.. Alternatively, the conversion of the phosphonate monoester **16.1** to the diester **16.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **16.2**
- 20 can be transformed into the phosphonate diester **16.1**, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a
- 25 two step procedure. In the first step, the phosphonate monoester **16.2** is transformed into the chloro analog RP(O)(OR¹)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product RP(O)(OR¹)Cl is then reacted with the hydroxy compound R¹OH, in the presence of a base such as triethylamine, to afford the phosphonate
- 30 diester **16.1**.

A phosphonic acid R-link-P(O)(OH)₂ can be transformed into a phosphonate monoester RP(O)(OR¹)(OH) (Scheme 16, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-P(O)(OR¹)₂ 16.1, except that only one molar proportion of the component R¹OH or R¹Br is employed. A phosphonic acid R-link-P(O)(OH)₂ 16.3 can be transformed into a phosphonate diester R-link-P(O)(OR¹)₂ 16.1 (Scheme 16, Reaction 6) by a coupling reaction with the hydroxy compound R¹OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R¹Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 16.1.

Scheme 16



Amprenavir-like phosphonate protease inhibitors (AMLPPi)**5 Preparation of the intermediate phosphonate esters 1-13.**

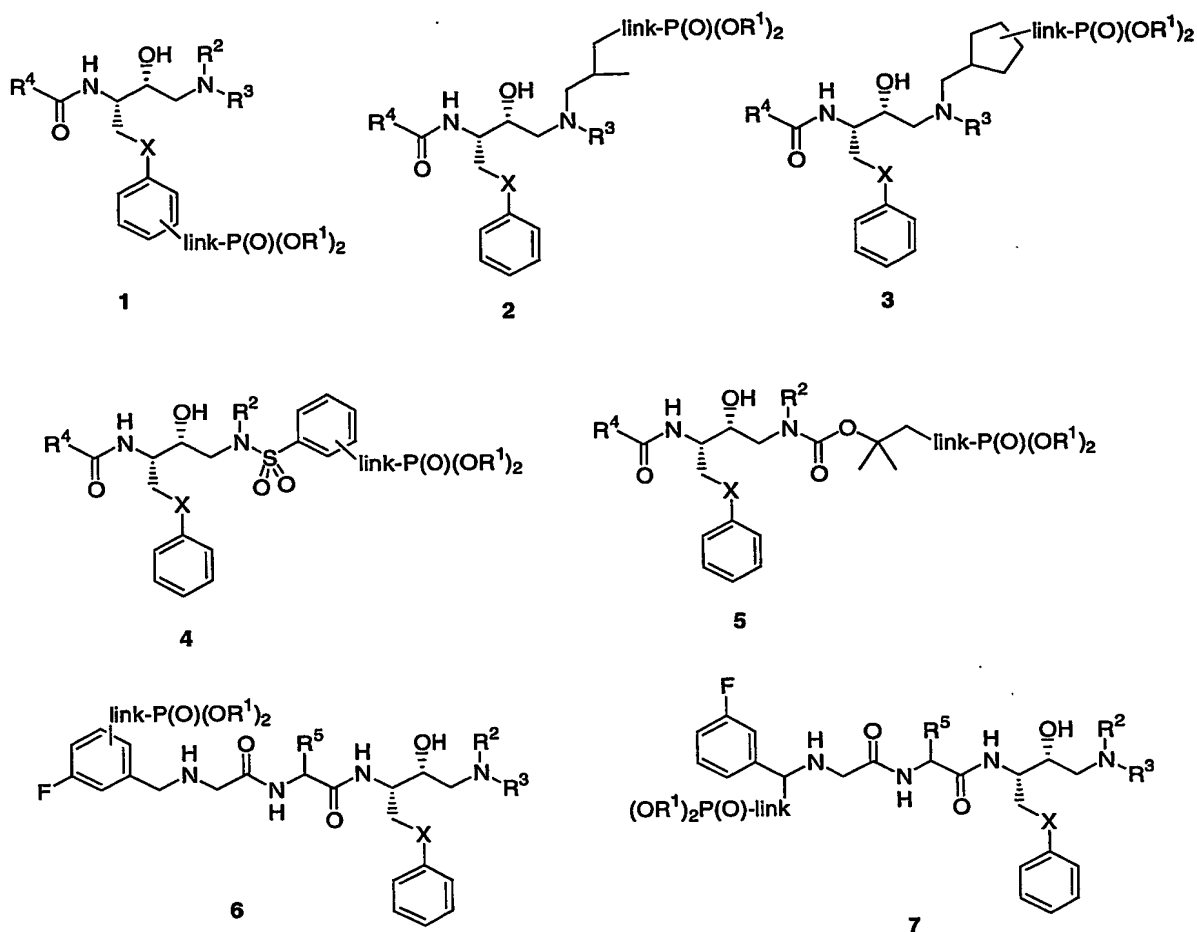
The structures of the intermediate phosphonate esters **1** to **13** and the structures of the component groups R^1 , R^5 , X of this invention are shown in Charts **1** - **2**. The structures of the R^2NH_2 components are shown in Chart **3**; the structures of the R^3-Cl components are shown
10 in Chart **4**; the structures of the R_4COOH groups are shown in Chart **5a-c**; and the structures of the $R^9CH_2NH_2$ amine components are illustrated in Chart **6**.

Specific stereoisomers of some of the structures are shown in Charts **1** - **6**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **13**. Subsequent chemical modifications to the compounds **1** to **10**, as described herein, permit the synthesis of the final
15 compounds of this invention.

The intermediate compounds **1** to **10** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7**, and **8** illustrate examples of the linking groups present in the structures **1** - **10**.

20 Schemes **1** - **99** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **10**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **11**, **12** and **13**, in which a phosphonate moiety is incorporated into one of the groups R^4 , R^3 , R^2 , respectively, is also described below.

Chart 1

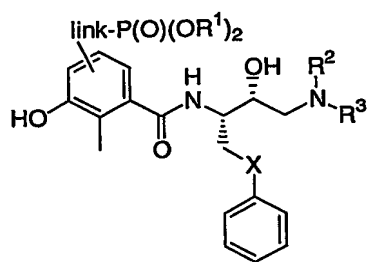


R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

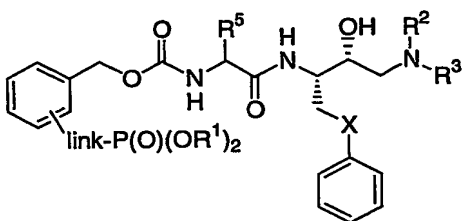
X = S or direct bond

R^5 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$, tert-butyl

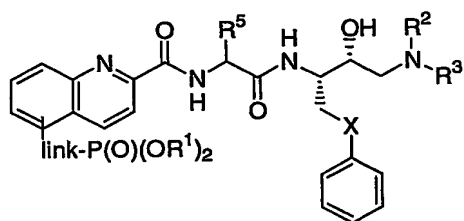
Chart 2



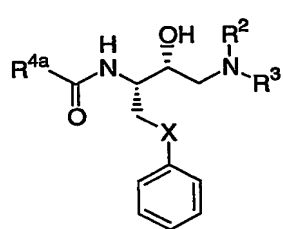
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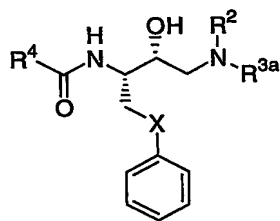
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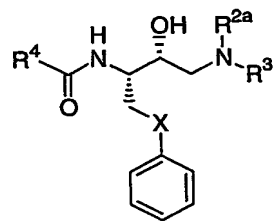
10

R^{4a} = phosphonate containing R⁴

11

R^{3a} = phosphonate containing R³

12

R^{2a} = phosphonate containing R²

13

R¹ = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

X = S or direct bond

R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, Imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

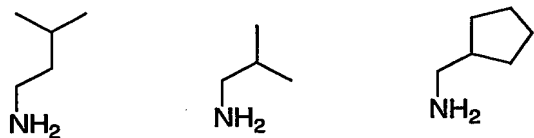
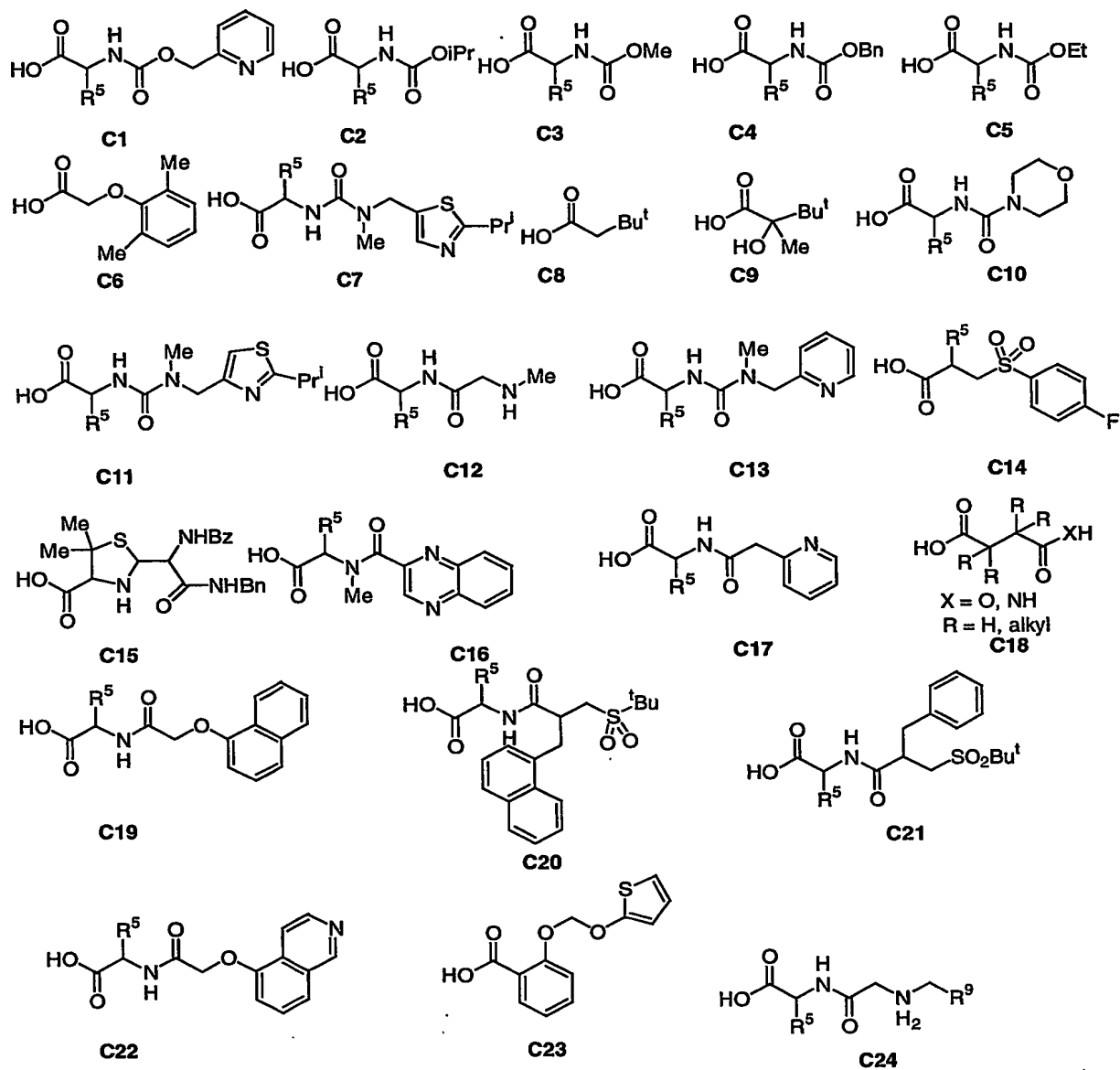
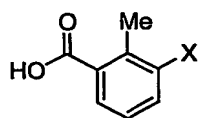
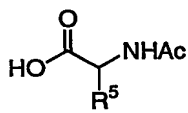
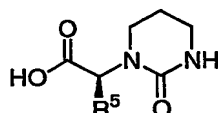
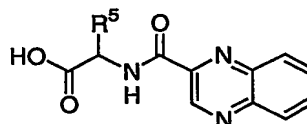
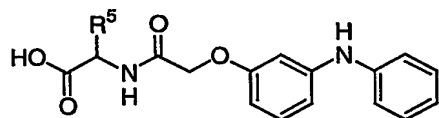
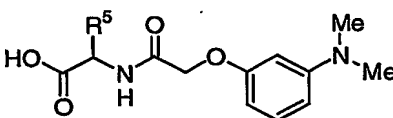
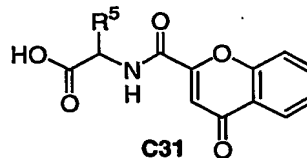
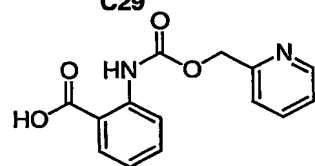
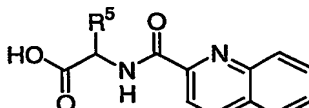
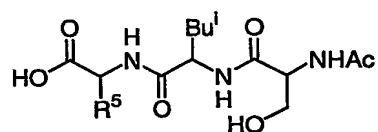
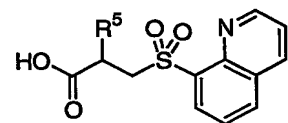
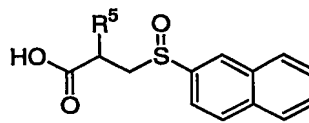
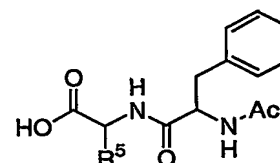
Chart 3 Structures containing the R²-NH₂ components**Chart 4 Structures containing the R³-Cl components**

Chart 5a Structures of the R⁴COOH components

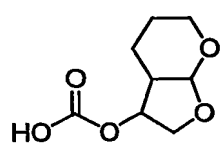
R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

Chart 5b Structures of the R⁴COOH components

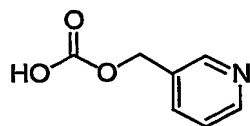
C25
X = OH, NH₂

**C26****C27****C28****C29****C30****C31****C32****C33****C34****C35****C36****C37**

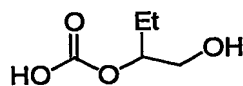
R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

Chart 5c Structures of the R⁴COOH components

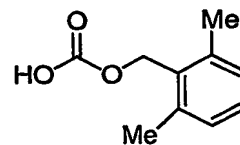
C38



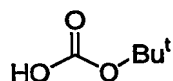
C39



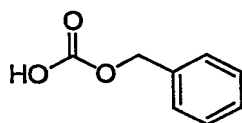
C40



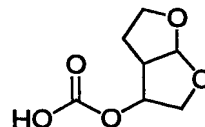
C41



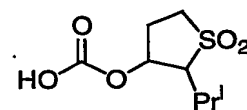
C42



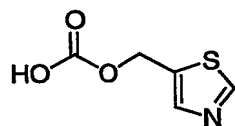
C43



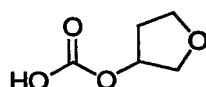
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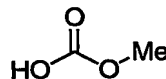
C45



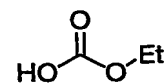
C46



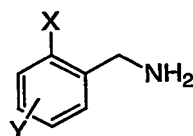
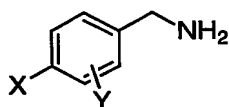
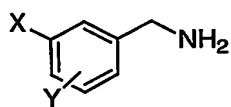
C47



C48



C49

Chart 6 Structures of the R⁹CH₂NH₂ components

X = F, Br, Cl ; Y = H, F, Br, Cl

Chart 7

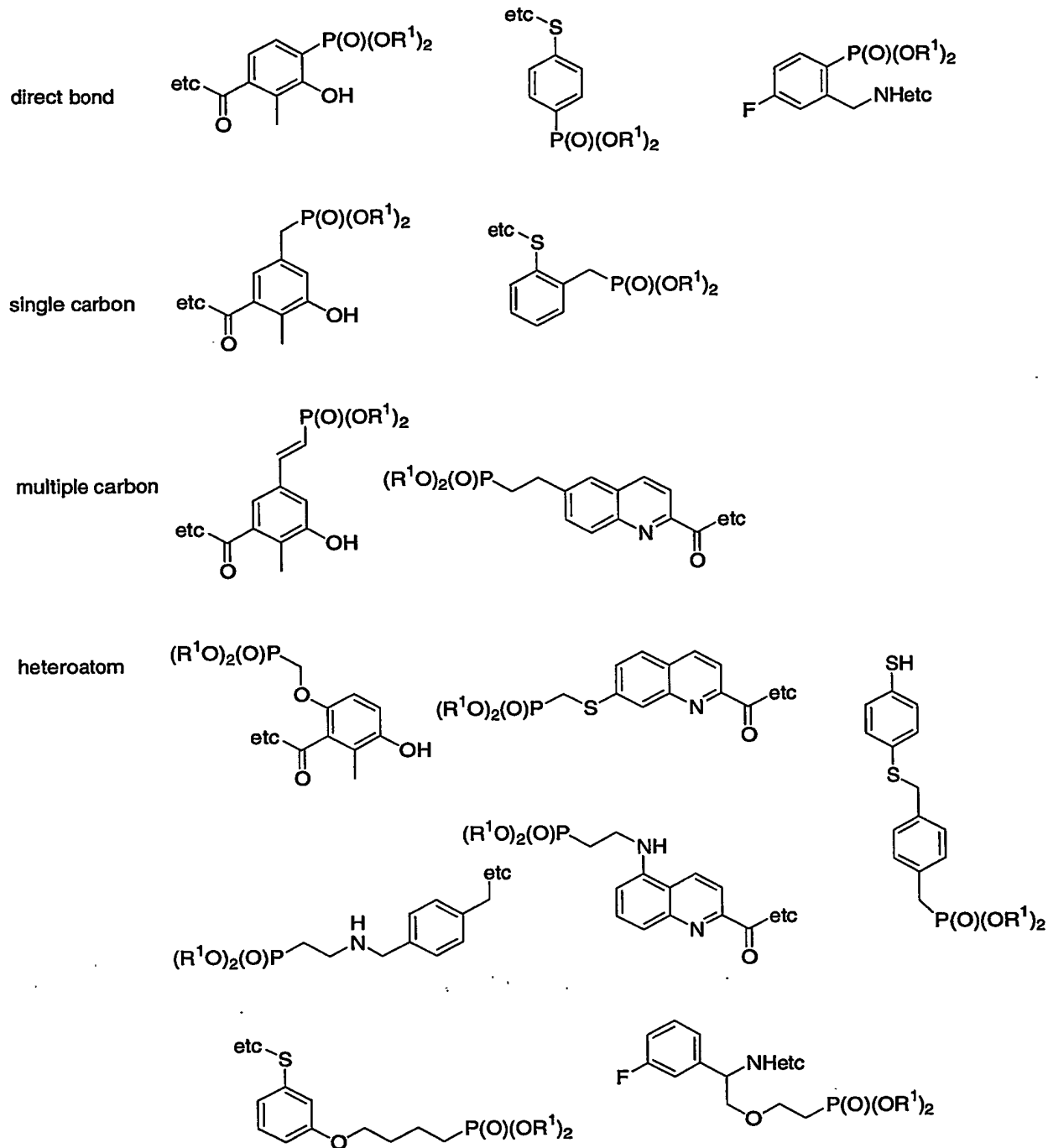
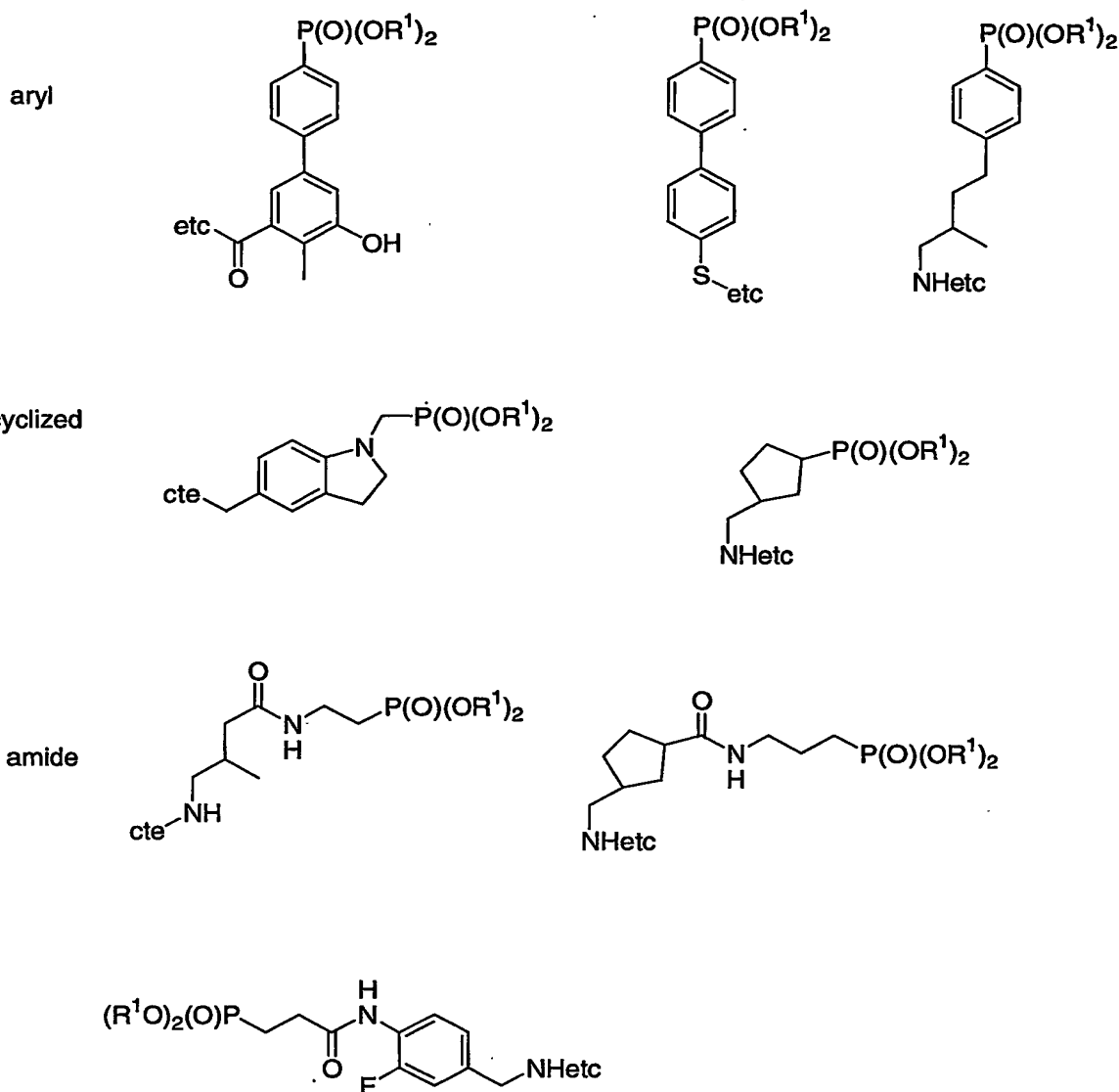


Chart 8



Protection of reactive substituents.

- 5 Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990
- 10 or Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the $R_4\text{COOH}$ group does not contain an secondary amine, and in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc are prepared as shown in Schemes 1-2. The epoxide 1.1 in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br is prepared as described in Schemes 56-59 below. Treatment of the epoxide 1.1 with the amine 1.2 affords the aminoalcohol 1.3. The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product 1.3. The amino alcohol 1.3 is then treated with an acylating agent 1.4 to afford the product 1.5. The acylating agent is typically a chloroformate or a sulfonyl chloride as shown in chart 4. Coupling conditions for amines with sulfonyl chlorides is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 603-615 or for chloroformates, p494ff. Preferably, the amine 1.3 is treated with the sulfonyl chloride 1.4 in the presence of a base such as pyridine, potassium carbonate etc and THF / water to give the product 1.5. Product 1.5 is deprotected using conditions described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 503ff. Preferably, the BOC amine is treated with TFA in an aprotic solvent such as THF. Conversion to the amide 1.8 is performed using standard coupling conditions between an acid 1.7 and the amine. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.7** is reacted with an equimolar amount of the amine **1.6** in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product **1.8**. The compound **1.8**, and analogous acylation products described below, in which the carboxylic acid R^4COOH is one of the carbonic acid derivatives **C38-C49**, as defined in Chart **5c**, are carbamates. Methods for the preparation of carbamates are described below, Scheme **98**.

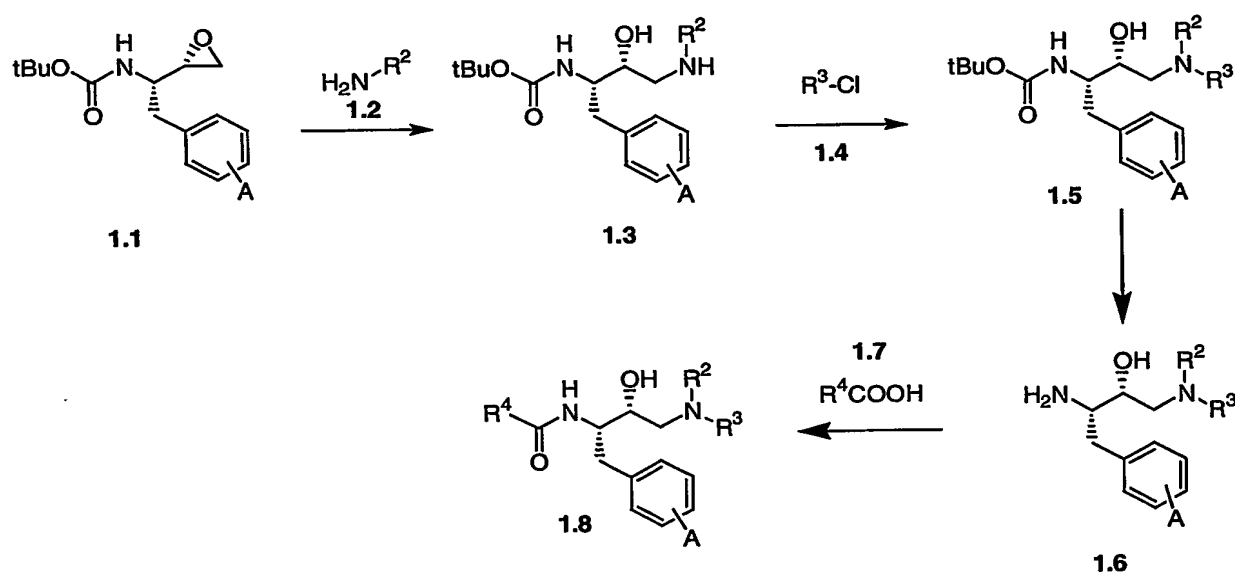
Scheme **2** illustrates an alternative method for the preparation of intermediate phosphonate esters **1**, in which the group A is attached to the aryl moiety, the R_4COOH group does not contain an secondary amine, and in which the substituent A is either the group link-

$P(O)(OR^1)_2$ or a precursor such as $[OH]$, $[SH]$, $[NH]$, Br etc. The oxazolidinone **2.1**, prepared as described in Schemes **60-62**, is first activated as shown in **2.2** and then treated with amine **1.2** to afford the secondary amine **2.3**. The hydroxyl group can be activated by converting into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative **2.2**, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product **2.2** is then reacted with the amine component **1.2** to afford the displacement product **2.3**.

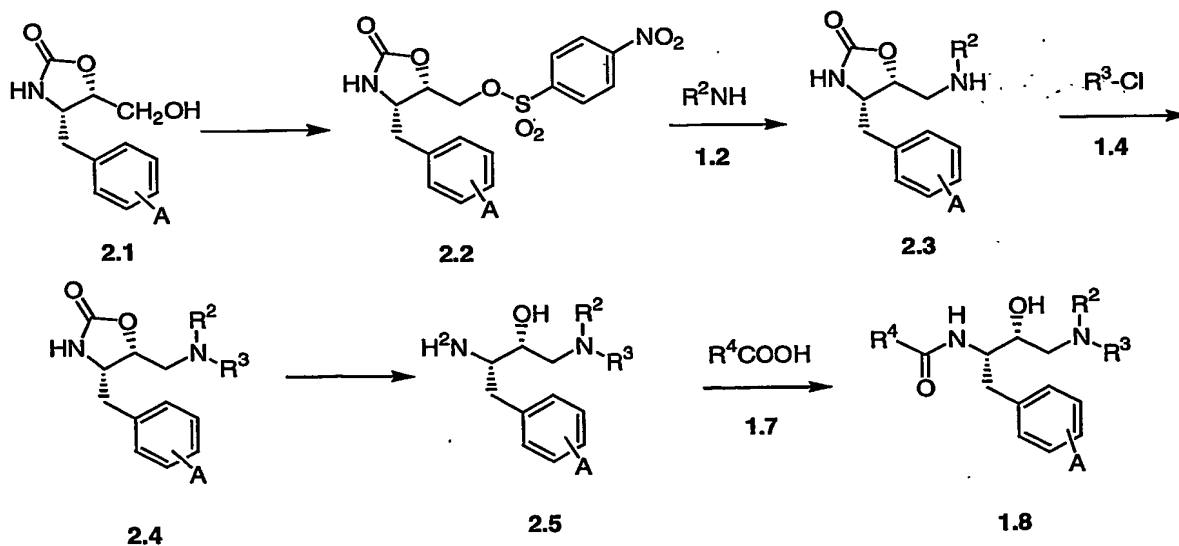
Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product **2.3**. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. Treatment of the amine product **2.3** with the R_3 chloride **1.4** as described in Scheme **1** then affords the product **2.4**. The oxazolidinone group present in the product **2.4** is then hydrolyzed to afford the hydroxyamine **2.5**. The hydrolysis reaction is effected in the presence of aqueous solution of a

base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound **2.4** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine **2.5**. This product is then reacted with the $R^4\text{COOH}$ carboxylic acid or activated derivative thereof, **1.7**, to afford the product **1.8**. The amide-forming reaction is conducted under the same conditions as described above, (Scheme 1).

Scheme 1



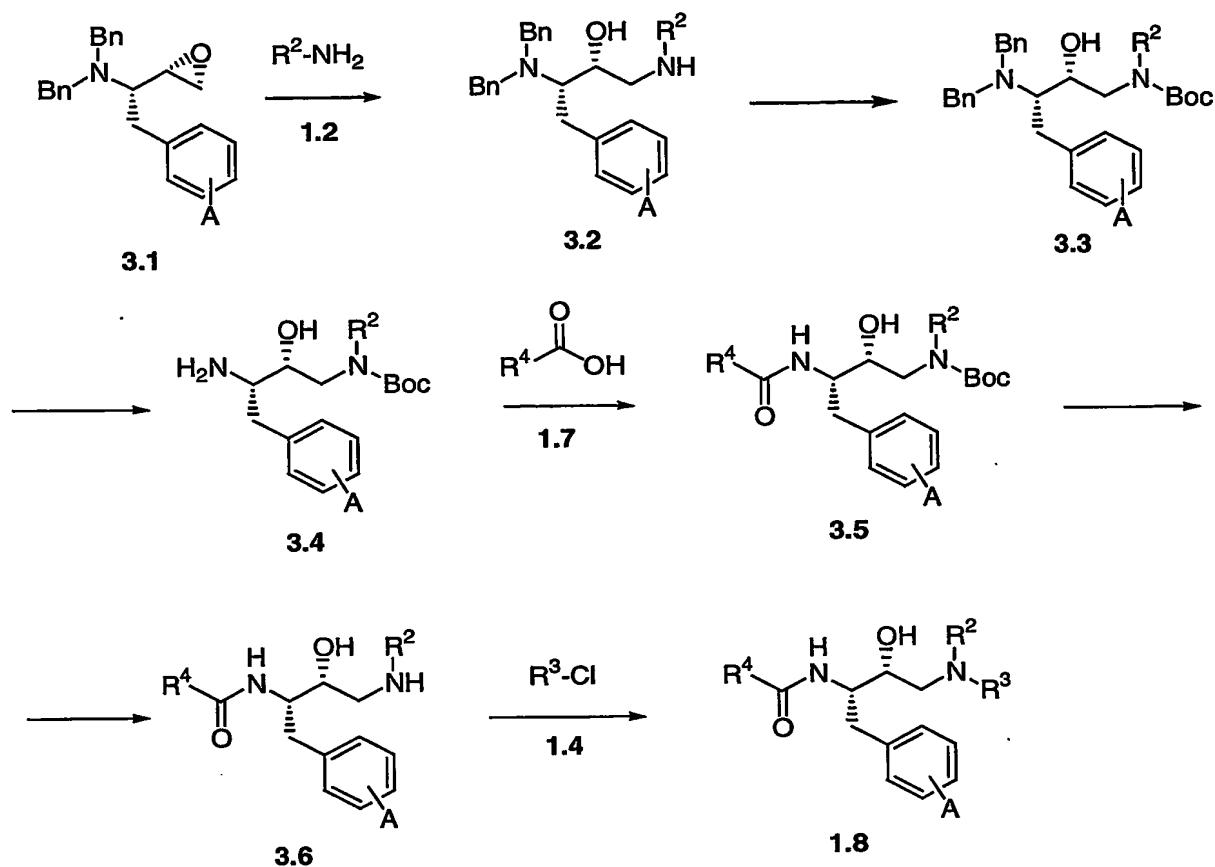
Scheme 2



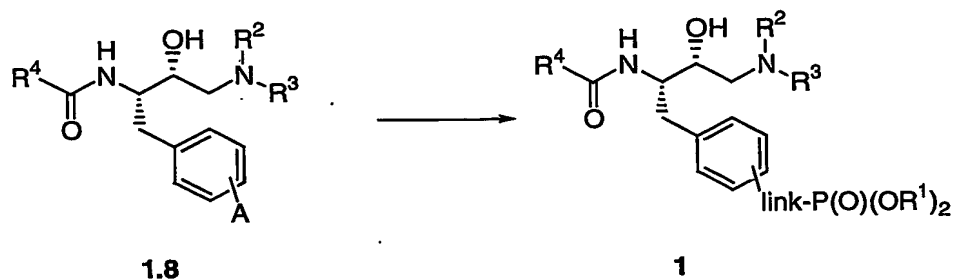
Scheme 3 illustrates the preparation of intermediate phosphonate esters **1**, in which the group A is attached to the aryl moiety, the R₄COOH group contains an secondary amine, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. The dibenzyl amine **3.2** is prepared from epoxide **3.1** and amine **1.2**,
5 following the same procedures described in Scheme 1 for the preparation of **1.3**. Epoxide **3.1** is prepared as described below in Schemes 56a. The amine **3.2** is then converted to the amine **3.4** as described in US6391919. Preferably, the amine is first protected as the BOC carbamate and then treated with palladium hydroxide on carbon (20%) in methanol under hydrogen at high pressure to give the amine **3.4**. Treatment of **3.4** with the R₄COOH acid **1.7** which
10 contains a secondary or primary amine, under standard amide bond forming conditions as described above, Scheme 1, then affords the amide **3.5**. Preferably, the acid **1.7**, EDC and n-hydroxybenzotriazole in DMF is treated with the amine **3.4** to give the amide **3.5**. Removal of the BOC group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 520-525 then affords the amine **3.6**. Preferably
15 the BOC amine **3.5** is treated with HCl in dioxane and water to give the free amine **3.6**. The amine **3.6** is then treated with an acylating agent such as an acid, chloroformate or sulfonyl chloride to give the final product **1.8**. Standard coupling conditions for amines with acids or sulfonyl chlorides is indicated above Scheme 1. Preferably, the amine **3.6** is treated with nitro-sulfonyl chloride in THF and water in the presence of a base such as potassium carbonate
20 to give the sulfonamide **1.8**.

The reactions shown in Scheme 1-3 illustrate the preparation of the compound **1.8** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 4 depicts the conversion of **1.8** in which A is [OH], [SH], [NH], Br etc,
25 into the phosphonate ester **1** in which X is a direct bond. In this procedure **1.8** is converted, using the procedures described below, Schemes 47-99, into the compound **1**. Also, in the preceding and following Schemes, the amino substituted sulfonamide reagents are typically introduced as a nitro-sulfonamide reagents. Therefore, where appropriate, an additional step of nitro group reduction as described in Comprehensive Organic Transformations, by R. C.
30 Larock, 2nd Edition, 1999, p.821ff, is performed to give the final amino products.

Scheme 3



Scheme 4



Scheme 5 illustrates an alternative method for the preparation of the compound 1 in which the group A is attached to the aryl moiety, the R_4COOH group contains a primary or secondary amine and in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine 3.4, (Scheme 3) is treated with an amino acid 5.1

under typical amide bond forming conditions to give the amide **5.2** as described above, Scheme **1**. Preferably the acid **5.1** is first treated with EDC and *n*-hydroxybenzotriazole in DMF and then the amine **3.4** is added in DMF followed by *N*-methyl morpholine to give the amide **5.2**. Reduction of the amide under the same catalytic hydrogenation conditions as described above in Scheme **3** gives the free amine **5.3**. The amine is further treated with chloroacetyl chloride to provide the chloro compound **5.4**. Preferably treatment with the chloroacetyl chloride is performed in ethyl acetate and water mixture in the presence of a base such as potassium hydrogen carbonate. The chloro compound **5.4** is treated with hydrochloric acid in dioxane and ethyl acetate to give the salt of the free amine **5.5**. The salt **5.5** is then treated with a nitro-sulfonyl chloride **1.4** in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide **5.6**. Alternatively the free amine **5.5** is treated with a chloroformate **1.4** in the presence of a base such as triethylamine to afford the carbamate. Methods for the preparation of carbamates are also described below, Scheme **98**. Compound **5.6** is then treated with the amine **5.7** to give the secondary amine **5.8**. Preferably the chloride is refluxed in the presence of the amine **5.7** in THF.

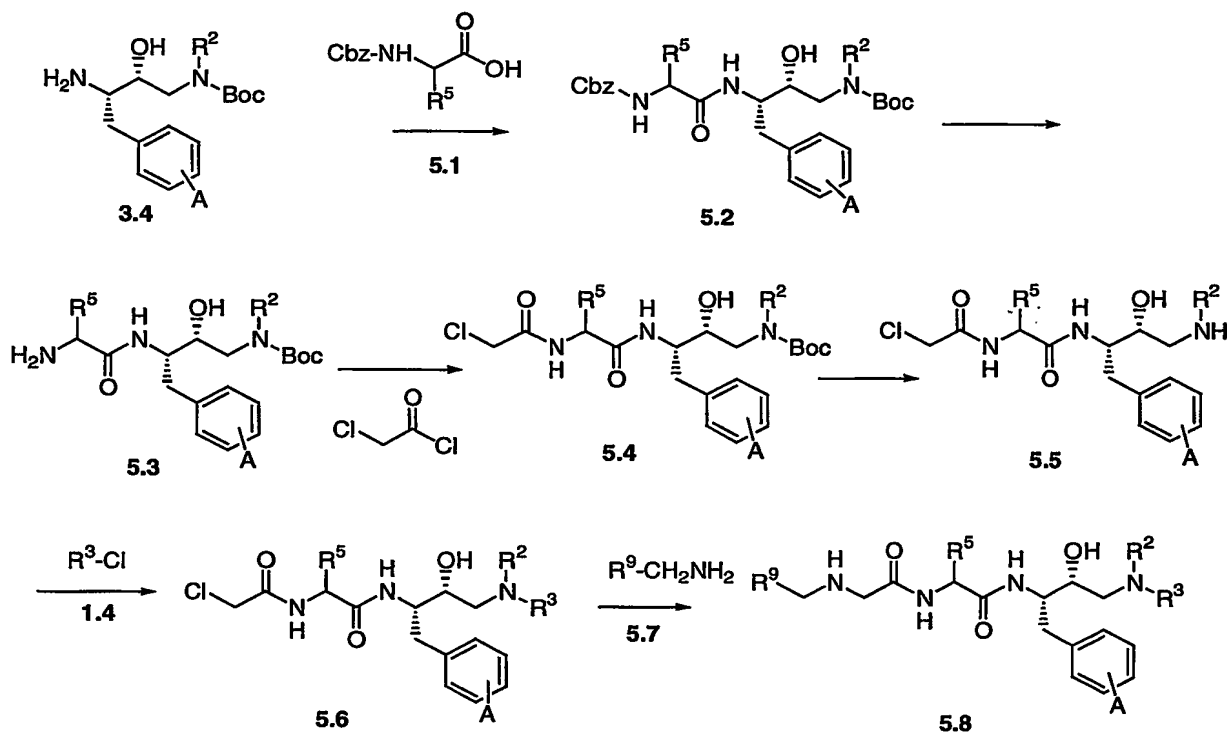
The reactions shown in Scheme **5** illustrate the preparation of the compound **5.8** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **6** depicts the conversion of **5.8** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **1** in which X is a direct bond. In this procedure **5.8** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**.

In the preceding and following schemes, the conversion of various substituents into the group link-P(O)(OR¹)₂ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-P(O)(OR¹)₂.

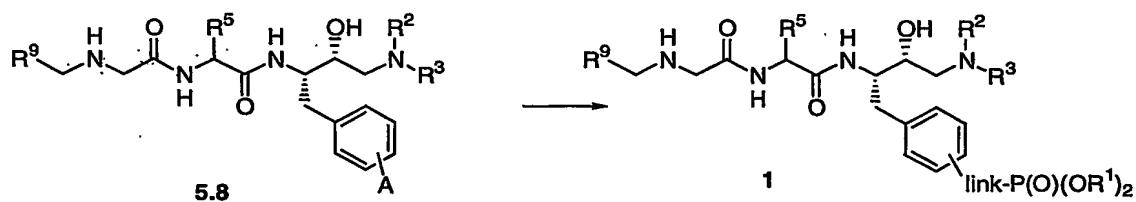
In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 99).

Scheme 5



Scheme 6



5

Preparation of the phosphonate ester intermediates 1 in which X is a sulfur.

The intermediate phosphonate esters 1, in which X is sulfur, the R₄COOH group does not contain a amine group, and in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, are prepared as shown in Schemes 7-9.

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Scheme 7 illustrates one method for the preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 7.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol 7.2 to afford the thioether 7.3. The preparation of thiol 7.2 is described in Schemes 63-72. The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether 7.3. Preferably the mesylate 7.1 is reacted with an equimolar amount of the thiol, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product 7.3. The 1,3-dioxolane protecting group present in the compound 7.3 is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol 7.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 7.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 7.3 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product 7.4. The primary hydroxyl group of the diol 7.4 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base. Preferably, equimolar amounts of the diol 7.4 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester 7.5. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester 7.6. Preferably, equimolar amounts of the carbinol 7.5 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 7.6. The compound 7.6 is then subjected to a hydrolysis-

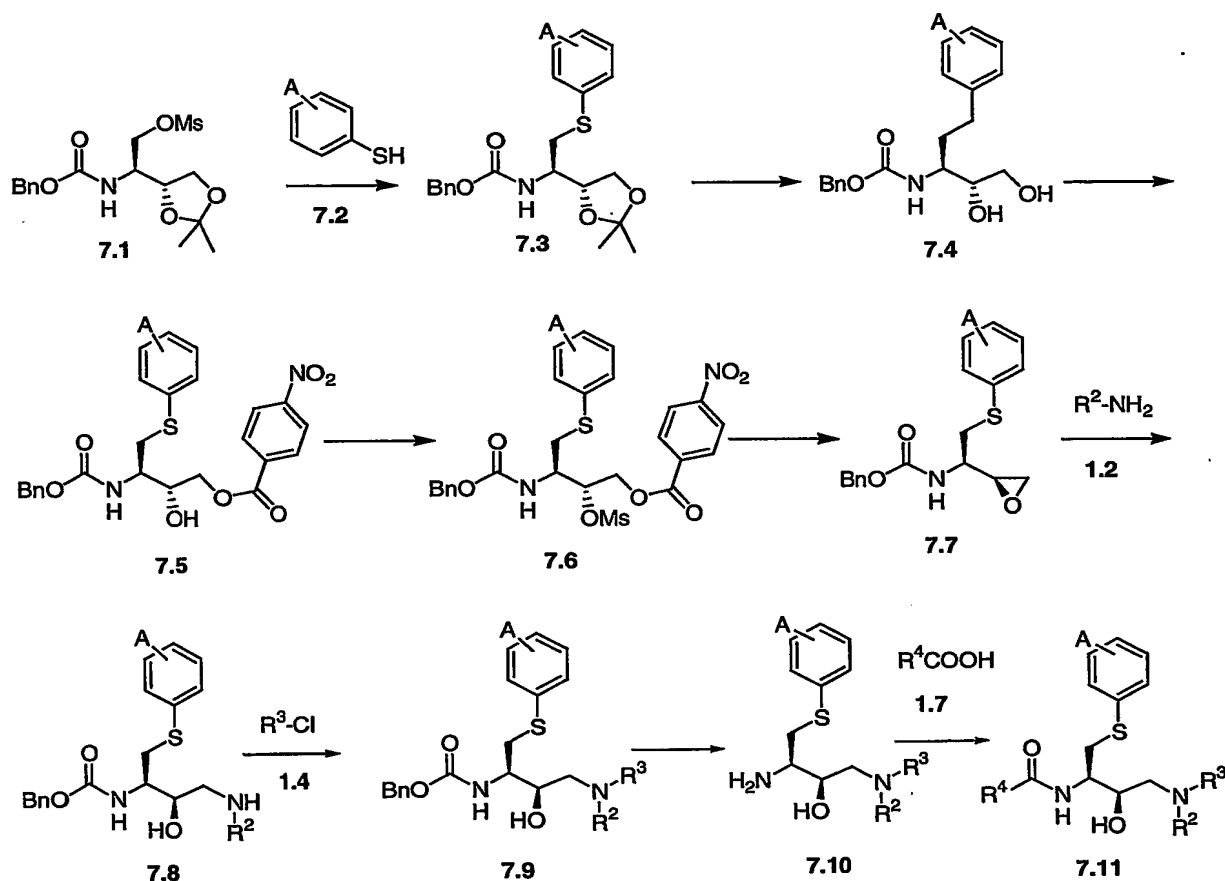
cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or
5 tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the
10 oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol **7.8**. The free amine is then substituted by treatment with an acid,

15 chloroformate or sulfonyl chloride as described above in Scheme 1 to give the amine **7.9**. The carbobenzyloxy (cbz) protecting group in the product **7.9** is removed to afford the free amine **7.10**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis. For example, the cbz-protected
20 amine **7.9** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **7.10**. Preferably, the cbz group is removed by the reaction of **7.9** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine **7.10**. The amine **7.10** so obtained is next acylated with a carboxylic acid or activated derivative **1.7**, using the conditions described above in Scheme 1 to afford the

25 product **7.11**

Scheme 7



Scheme 8 illustrates an alternative preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, 4-amino-tetrahydro-furan-3-ol, 8.1, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R⁴COOH, 1.7, using the conditions described above for in Scheme 1 for the preparation of amides, to afford the amide 8.2. The amide product 8.2 is then transformed, using the sequence of reactions shown in Scheme 8, into the isoxazoline compound 8.5. The hydroxyl group on the tetrahydrofuran moiety in 8.2 is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane. Preferably, the hydroxy amide 8.2 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 8.3. The product 8.3, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 8.4. The

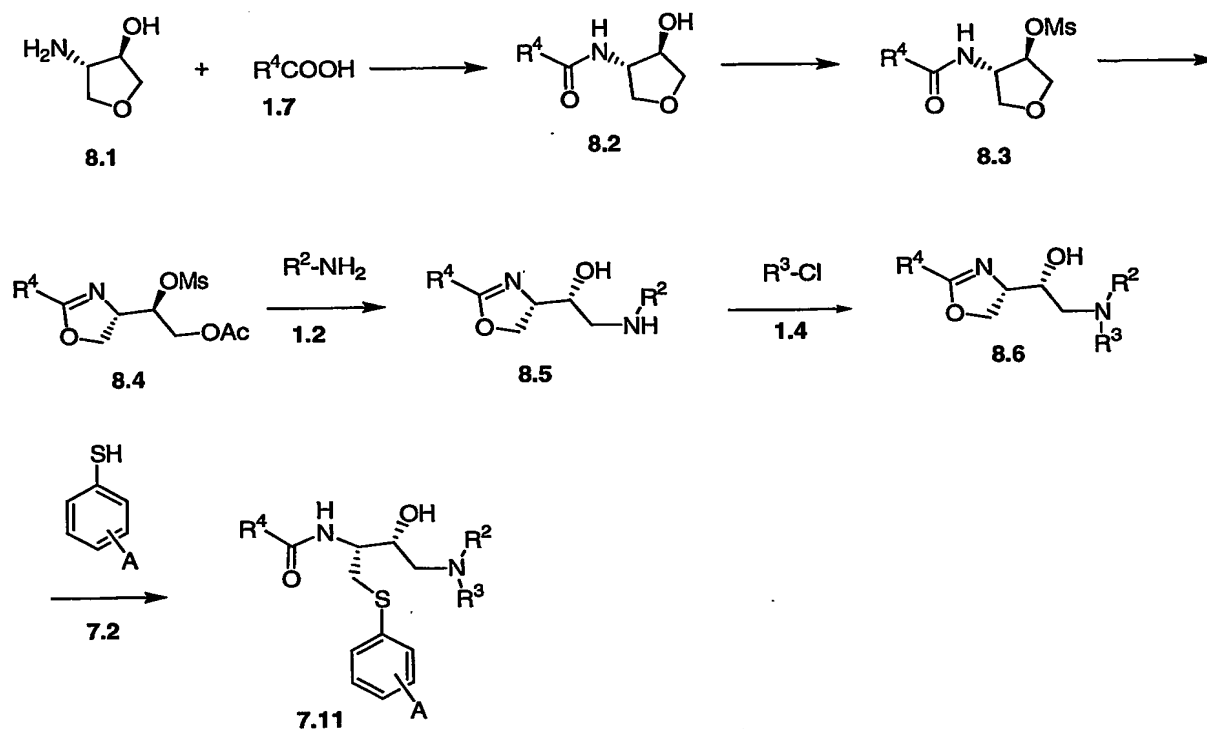
rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst. Preferably, the mesylate **8.3** is dissolved in an acylating agent such as acetic anhydride at about 0°C, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **8.4**. The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine. The compound **8.4** is reacted with an amine **1.2**, as defined in Chart 3, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **8.5**. Preferably, the mesylate compound **8.4** is reacted with an equimolar amount of the amine **1.2**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **8.5**. The product **8.5** is then treated with R³Cl, chart 6 as described above in Scheme 1 to afford the amine **8.6**. The compound **8.6** is then reacted with a thiol **7.2** to afford the thioether **7.11**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product **7.11**. Preferably, the isoxazoline **8.6** is reacted, in methanol, with an equimolar amount of the thiol **7.2**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **7.11**.

The procedures illustrated in Scheme 7-8 depict the preparation of the compounds **7.11** in which X is S, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc, as described below. Scheme 9 illustrates the conversion of compounds **7.11** in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds **1** in which X=S. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 47 – 99).

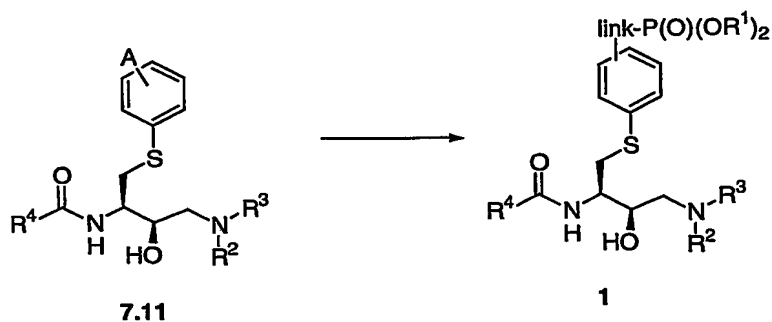
Scheme 9a-9b depicts the preparation of phosphonate esters **1**, in which X is sulfur, the R₄COOH group does contain a amine group, and in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. The amine **7.10** prepared in Scheme 7 is treated with the CBZ protected amine **5.1** using the same conditions described in Scheme 5 for the preparation of **5.2** to give CBZ amine **9a.1**. Removal of the CBZ group as described in Scheme 5 to give **9a.2** followed by treatment with chloroacetyl chloride as described in Scheme 5 gives chloride **9a.3**. The chloride **9a.3** is then treated with the amine **5.7** to give the amine **9a.4** as described in Scheme 5.

The reactions shown in Scheme 9a illustrate the preparation of the compound 9a.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 9b depicts the conversion of 9a.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 1 in which X is sulfur. In this procedure 9a.4 is converted, using the procedures described below, Schemes 47-99, into the compound 1.

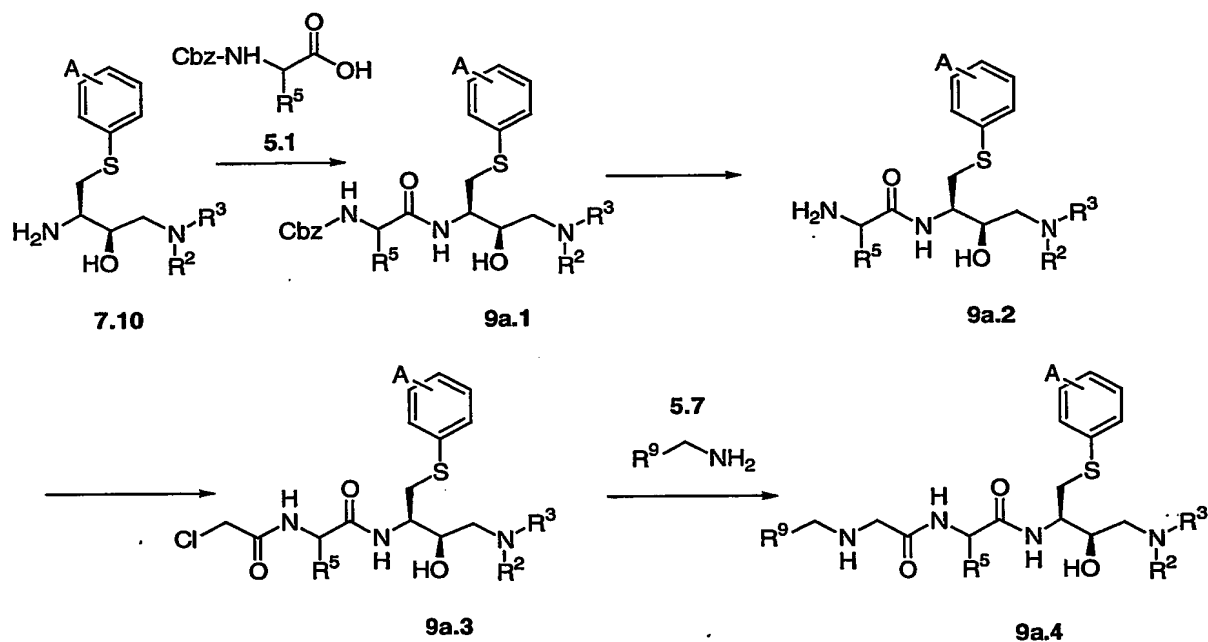
Scheme 8



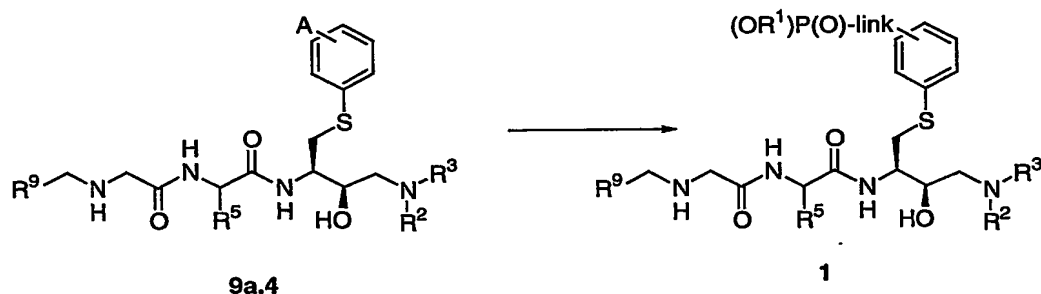
Scheme 9



Scheme 9a



Scheme 9b



Preparation of the phosphonate ester intermediates 2 and 3 in which X is a direct bond

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Schemes 10-12 illustrate the preparation of the phosphonate esters 2 and 3 in which X is a direct bond and the $R_4\text{COOH}$ group does not contain a primary or secondary amine group. As shown in Scheme 10, the epoxide 10.1, prepared as described in J. Med. Chem 1994, 37, 1758 is reacted with the amine 10.2 or 10.5, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine 10.3 and 10.6 respectively. The reaction is performed under the same conditions as described

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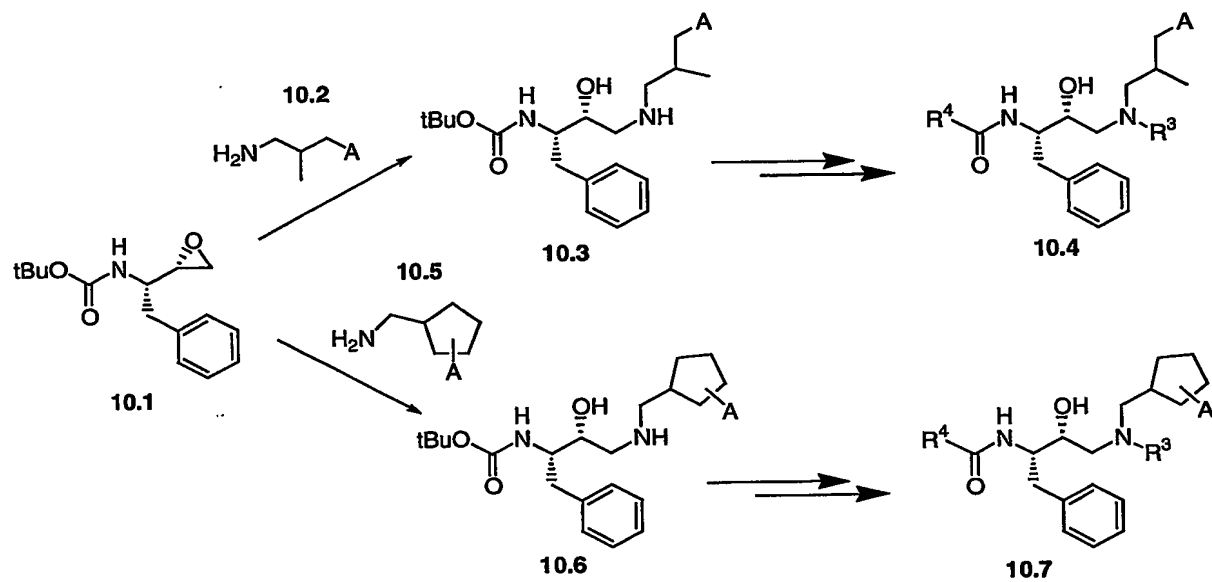
above, Scheme 1 for the preparation of the amine 1.3. The preparation of the amines 10.2 is described in Schemes 73-75 and amines 10.5 in schemes 76-78. The products 10.3 and 10.6 are then transformed, using the sequence of reactions described above, Scheme 1, for the conversion of the amine 1.3 into the amide 1.8, into the aminoamide 10.4 and 10.7

5 respectively.

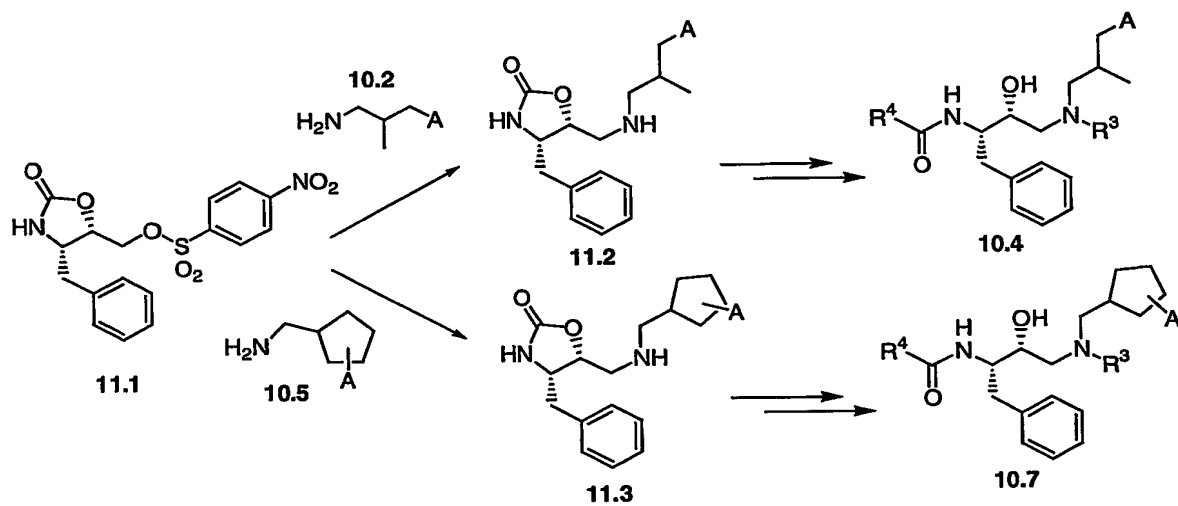
An alternative route to the amines 10.4 and 10.7 is shown in Scheme 11 in which sulfonyl ester 11.1 prepared according to Chimia 1996, 50, 532 is treated under conditions described in Scheme 2 with the amines 10.2 or 10.5 to give the amines 11.2 or 11.3 respectively. These
10 amine products are then converted as described above, Scheme 2, into the amides 10.4 and 10.7 respectively.

The reactions shown in Scheme 10 and 11 illustrate the preparation of the compounds 10.4 and 10.7 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as
15 [OH], [SH], [NH], Br etc. Scheme 12 depicts the conversion of these compounds 10.4 and 10.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2 and 3 respectively, in which X is a direct bond. In this procedure, the amines 10.4 and 10.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3 respectively.

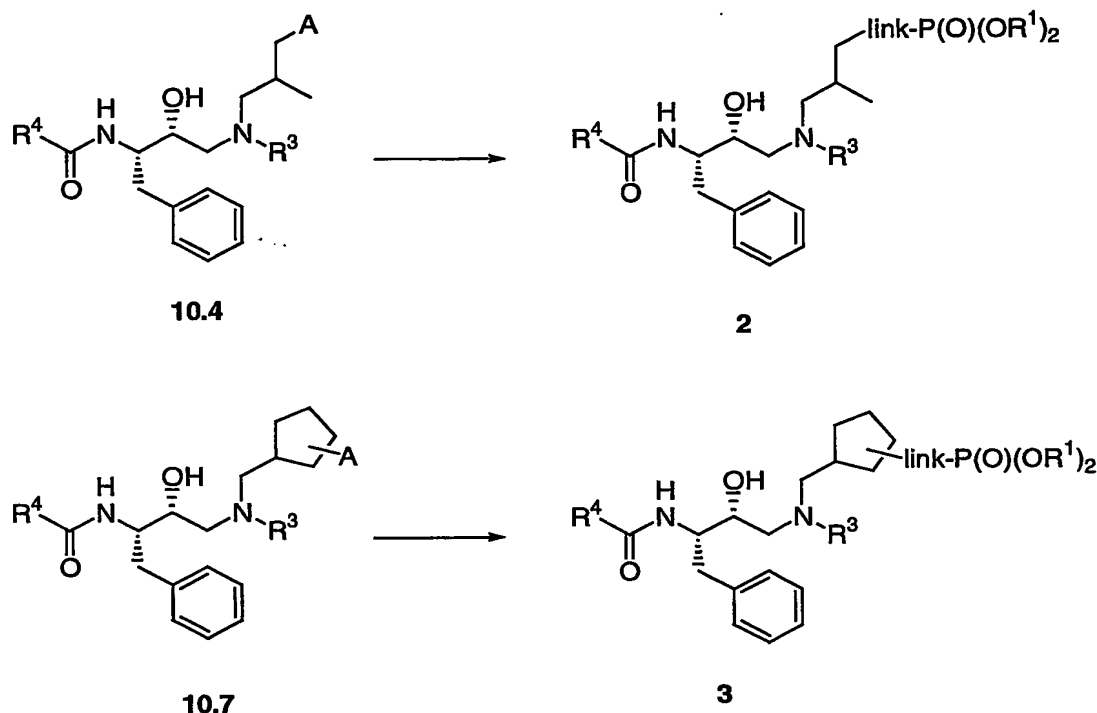
Scheme 10



Scheme 11



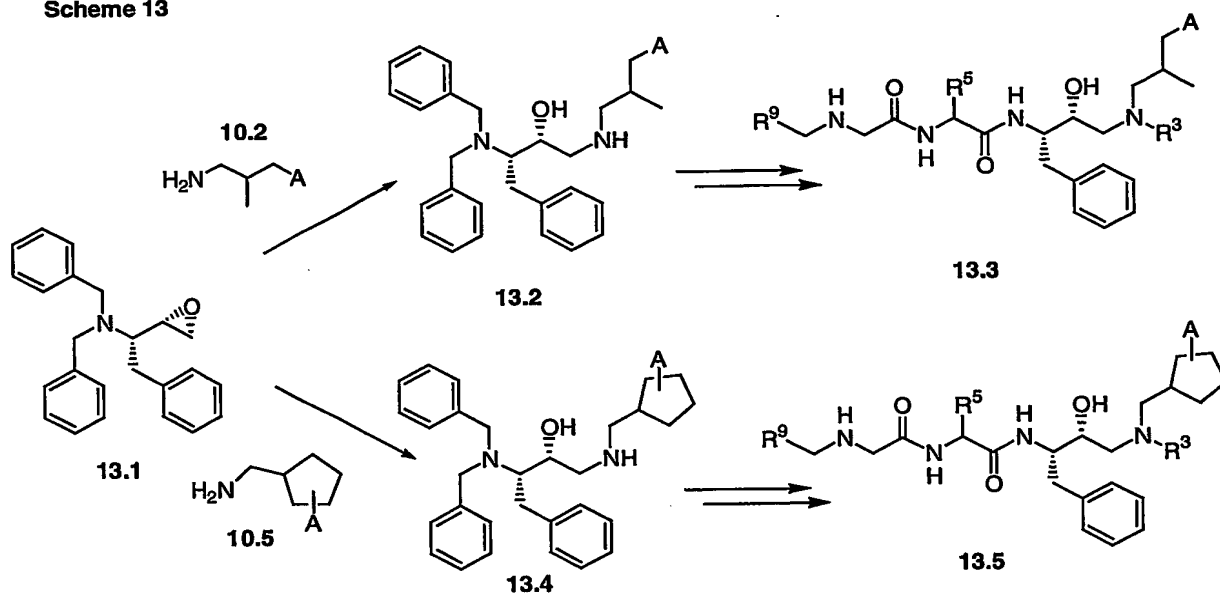
Scheme 12



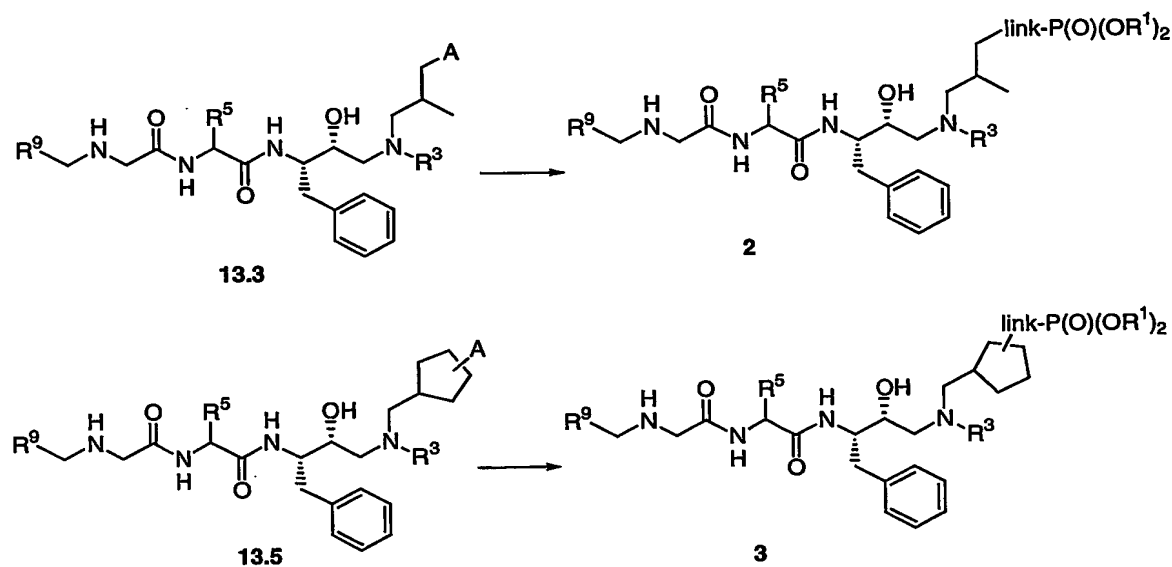
Schemes 13-14 illustrates the preparation of the phosphonate esters 2 and 3 in which X is a direct bond and the R_4COOH group contains an amine. The epoxide 13.1, prepared as described in US 6391919B1, or J. Org. Chem. 1996, 61, 3635 is reacted, as described above, (Scheme 1) with the amine 10.2 or 10.5, in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc, to give the amino alcohols 13.2 and 13.4, respectively. These amines are then converted as described in Scheme 3 for the conversion of 3.2 into 3.4 and Scheme 5 for the conversion of 3.4 into 5.8, into the amine products 13.3 and 13.5 respectively.

The reactions shown in Scheme 13 illustrate the preparation of the compounds 13.3 and 13.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc. Scheme 14 depicts the conversion of the compounds 13.3 and 13.5 in which A is $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc, into the phosphonate esters 2 and 3 in which X is a direct bond. In this procedure, the compounds 13.3 and 13.5 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3 respectively.

Scheme 13



Scheme 14



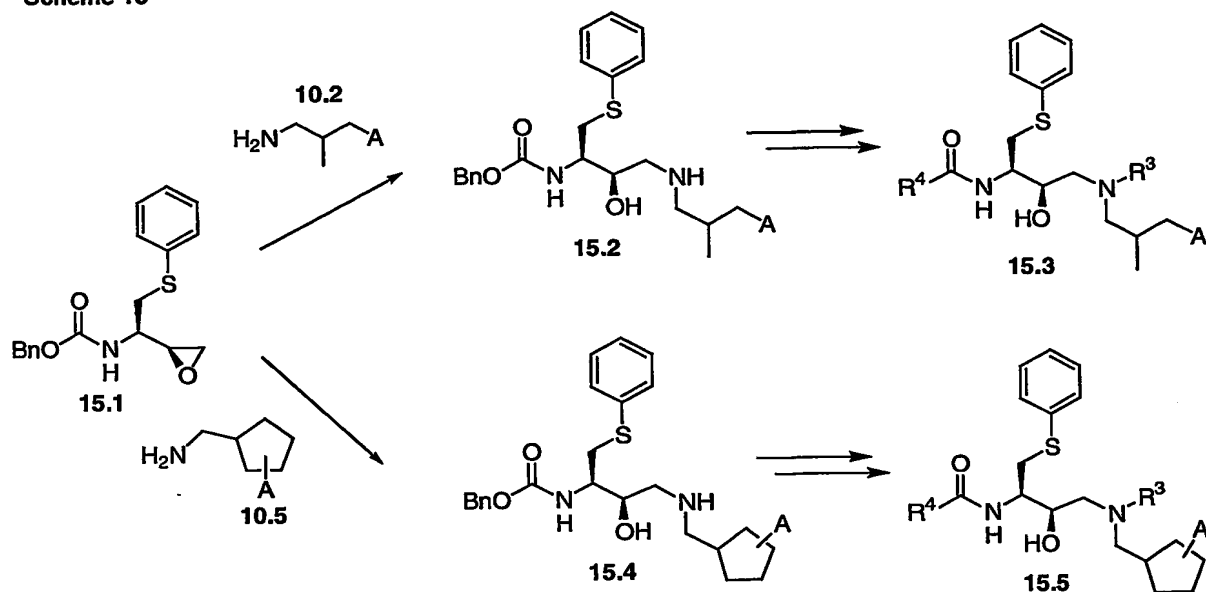
Preparation of the phosphonate ester intermediates 2 and 3 in which X is a sulfur

- 5 The intermediate phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group does not contain an amine group, are prepared as shown in Schemes 15-17. In Scheme 15, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 for the preparation of 7.7 from 7.1, except incorporating

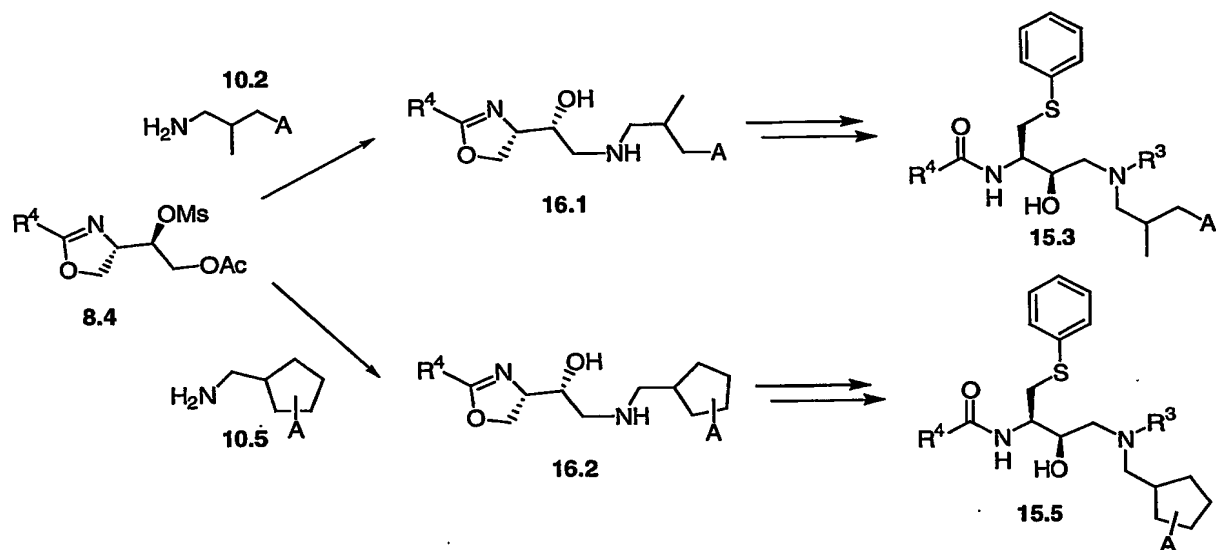
thiophenol for thiol 7.2. The epoxide 15.1 is then treated with amine 10.2 or amine 10.5, in which substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amines 15.2 and 15.4. Further application of Scheme 7 on the amines 15.2 and 15.4 yields the alcohols 15.3 and 15.5 respectively.

- 5 Alternatively, Scheme 16 depicts the preparation of 15.3 and 15.5 using the mesylate 8.4. The amines 10.2 and 10.5 are reacted with mesylate 8.4 under conditions described in Scheme 8 to give amines 16.1 and 16.2 respectively. Further modification of 16.1 and 16.2 according to the conditions described in Scheme 8 then affords alcohols 15.3 and 15.5 respectively.
- 10 The reactions shown in Scheme 15-16 illustrate the preparation of the compounds 15.3 and 15.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 17 depicts the conversion of 15.3 and 15.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 in which X is sulfur. In this procedure 15.3 or 15.5 is converted, using the procedures described below, Schemes 47-99,
- 15 into the compound 2 and 3.

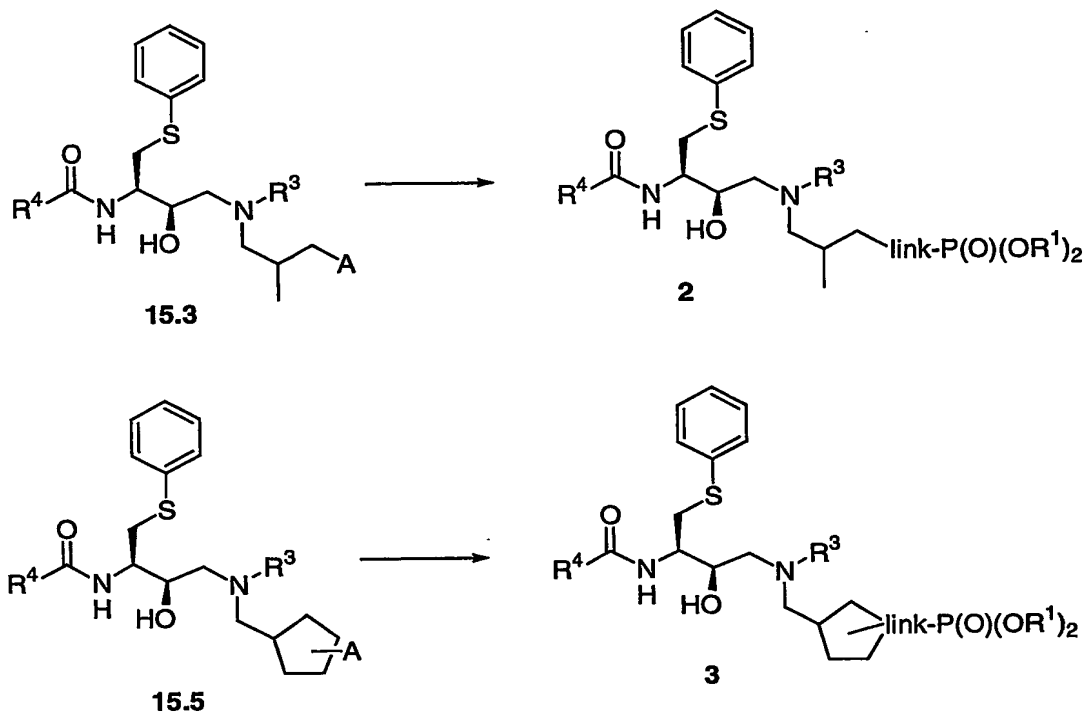
Scheme 15



Scheme 16



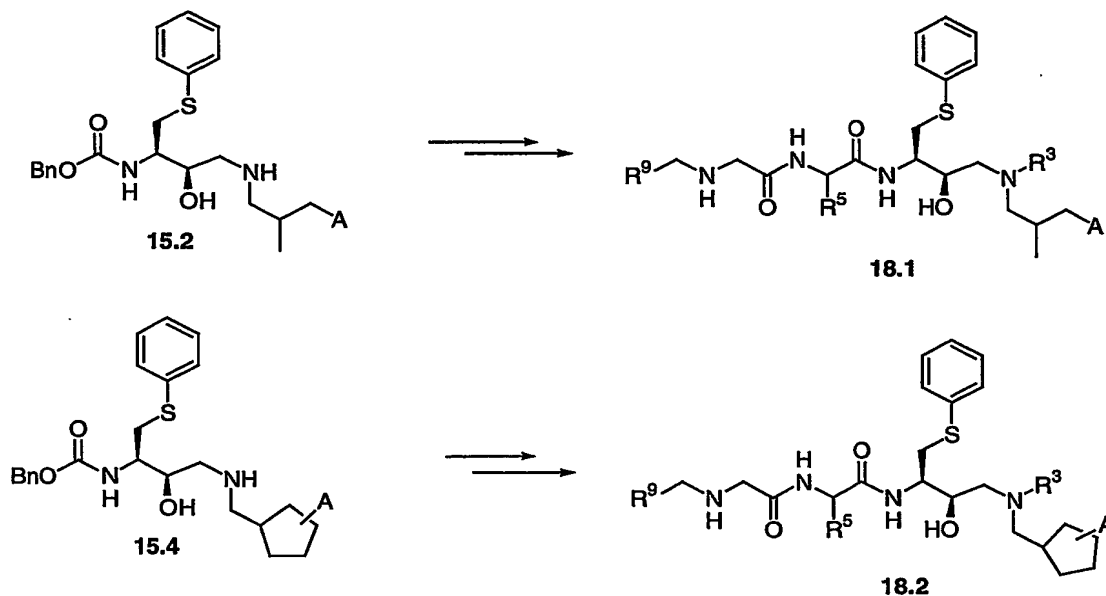
Scheme 17



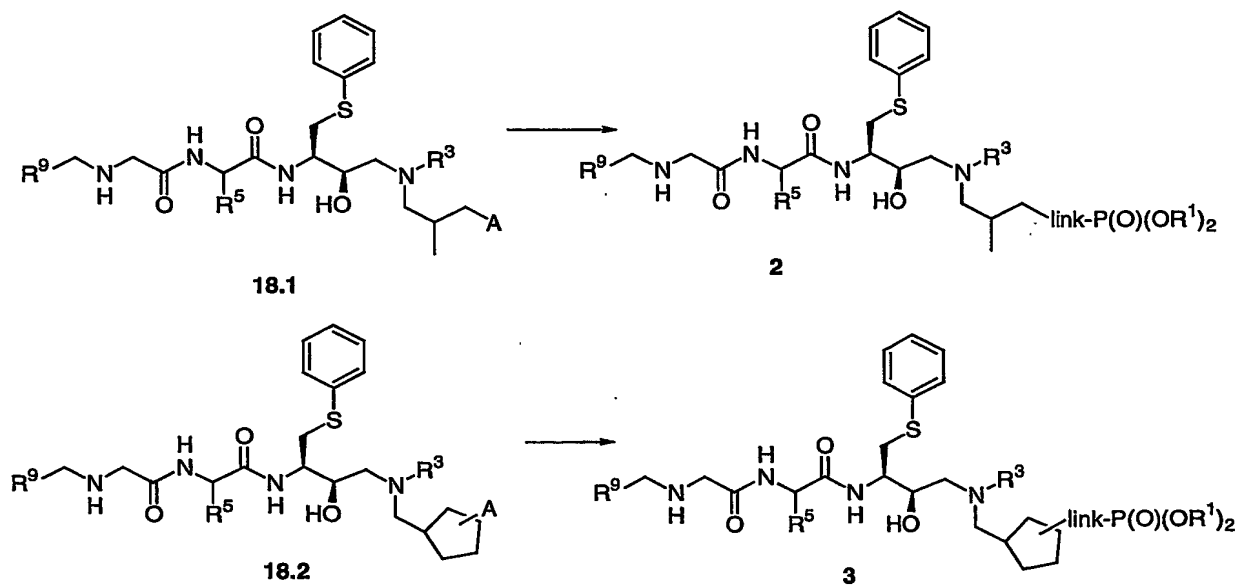
Scheme 18-19 depict the preparation of phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains a amine group. The amines 15.2 and 15.4, in which substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, prepared in Scheme 15, are converted using the same conditions described in Scheme 7 for the preparation of the amine 7.10 from 7.8 and Scheme 9a for the preparation of 9a.4 from 7.10 to give 18.1 and 18.2 respectively.

The reactions shown in Scheme 18 illustrate the preparation of the compound 18.1 and 18.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 19 depicts the conversion of 18.1 and 18.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 respectively in which X is sulfur. In this procedure 18.1 and 18.2 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3

Scheme 18



Scheme 19



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond

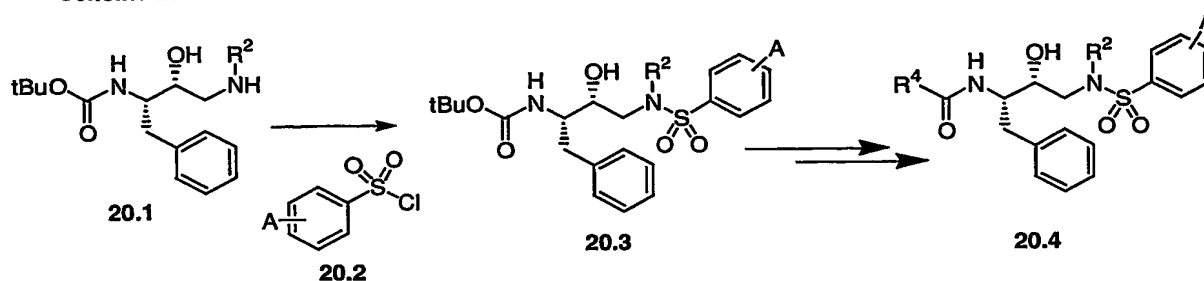
- 5 Schemes 20-22 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 20, the amine 20.1 is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to

afford the product **20.3**. The reaction is performed under the same conditions as described above, Scheme **1** for the preparation of the sulfonamide **1.5**. Amine **20.1** is prepared by treatment of epoxide **10.1** with the amine **1.2** as described in Scheme **1** for the preparation of **1.3**. The preparation of sulfonyl chloride **20.2** is described in Schemes **92-97**. The product
5 **20.3** is then transformed, using the sequence of reactions described above, Scheme **1**, for the conversion of the amide **1.5** into the amide **1.8**, into the product **20.4**.

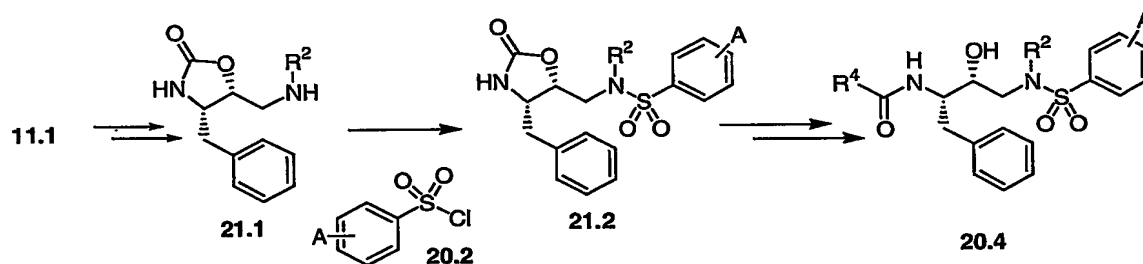
An alternative route to the product **20.4** is shown in Scheme **21** in which amine **11.1** is treated under conditions described in Scheme **2** with the amine **1.2** to give the amine **21.1**. The amine
10 **21.1** is then sulfonylated with **20.2** in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **2**, to afford the product **21.2**. The product **21.2** is then converted as described above, Scheme **2**, into the sulfonamide **20.4**.

15 The reactions shown in Scheme **20** and **21** illustrate the preparation of the compound **20.4** in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **22** depicts the conversion of this compounds **20.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4** respectively, in which X is a direct bond. In this procedure, the amines **20.4** is converted, using the procedures described below,
20 Schemes **47-99**, into the compounds **4**.

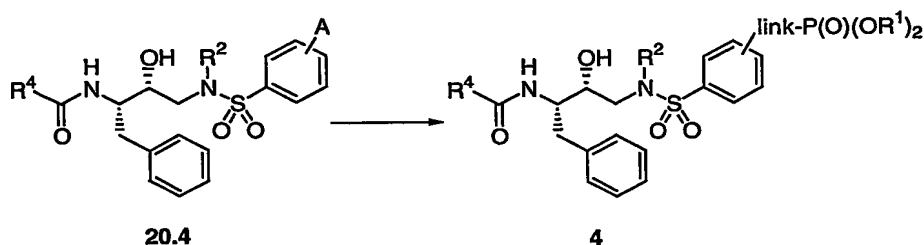
Scheme 20



Scheme 21



Scheme 22

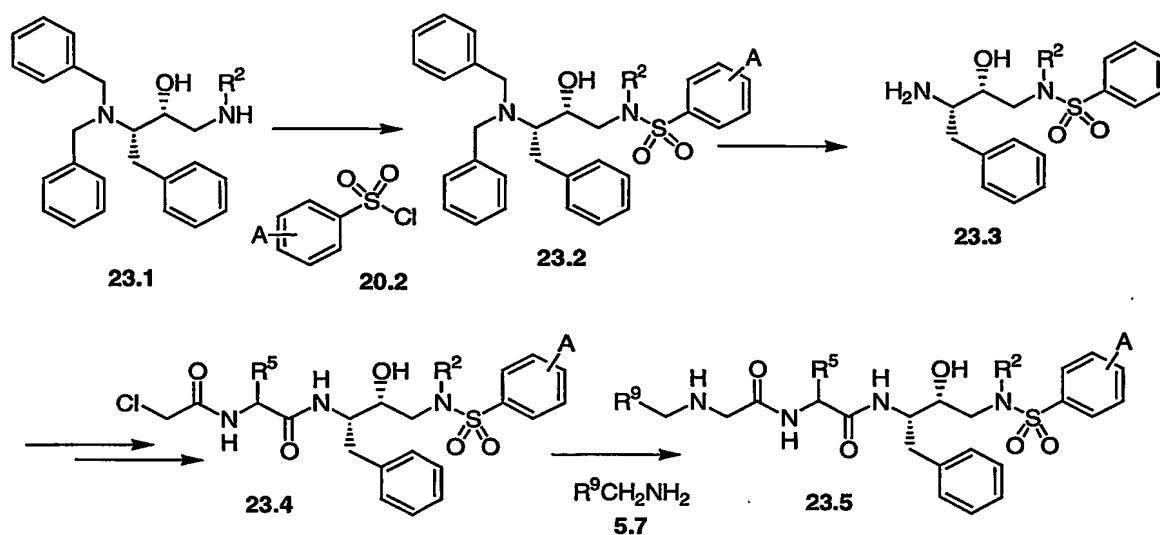


Schemes 23 illustrates the preparation of the phosphonate esters 4 in which X is a direct bond and the R₄COOH group contains an amine group. The amine 23.1, prepared from the epoxide 13.1 and an amine 1.2 as described in Scheme 13 for the synthesis of 13.2 from 13.1, is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Schemes 1 for the synthesis of 1.5, to give the product 23.2. The product 23.2 is then reduced to amine 23.3 according to the conditions described in Scheme 3 for the preparation of 3.4 from 3.3. The amine product is then converted as described in Scheme 5 into the chloride 23.4. The chloride is treated with the amine 5.7 to afford the amine 23.5, as described in Scheme 5 for the preparation of 5.8 from 5.7.

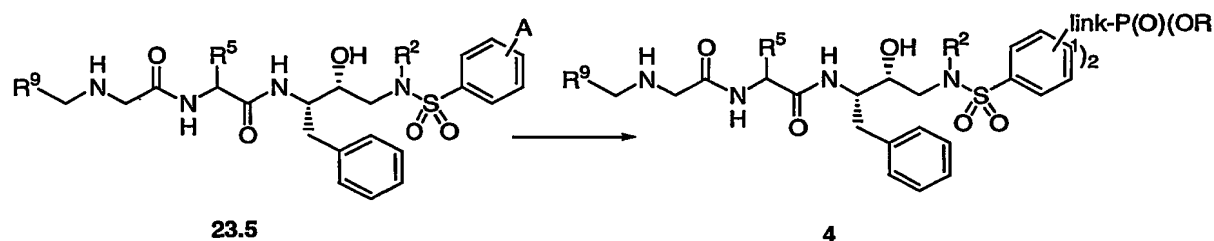
The reactions shown in Scheme 23 illustrate the preparation of the compound 23.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 24 depicts the conversion of the compound 23.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4 in which X is a direct bond. In this

5 procedure, the compound 23.5 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

Scheme 23



Scheme 24



10 Preparation of the phosphonate ester intermediates 4 in which X is a sulfur

The intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group does not contain an amine is prepared as shown in Schemes 25-27. Amine 25.1 prepared from epoxide 15.1 and amine 1.2 as described in Scheme 15 is

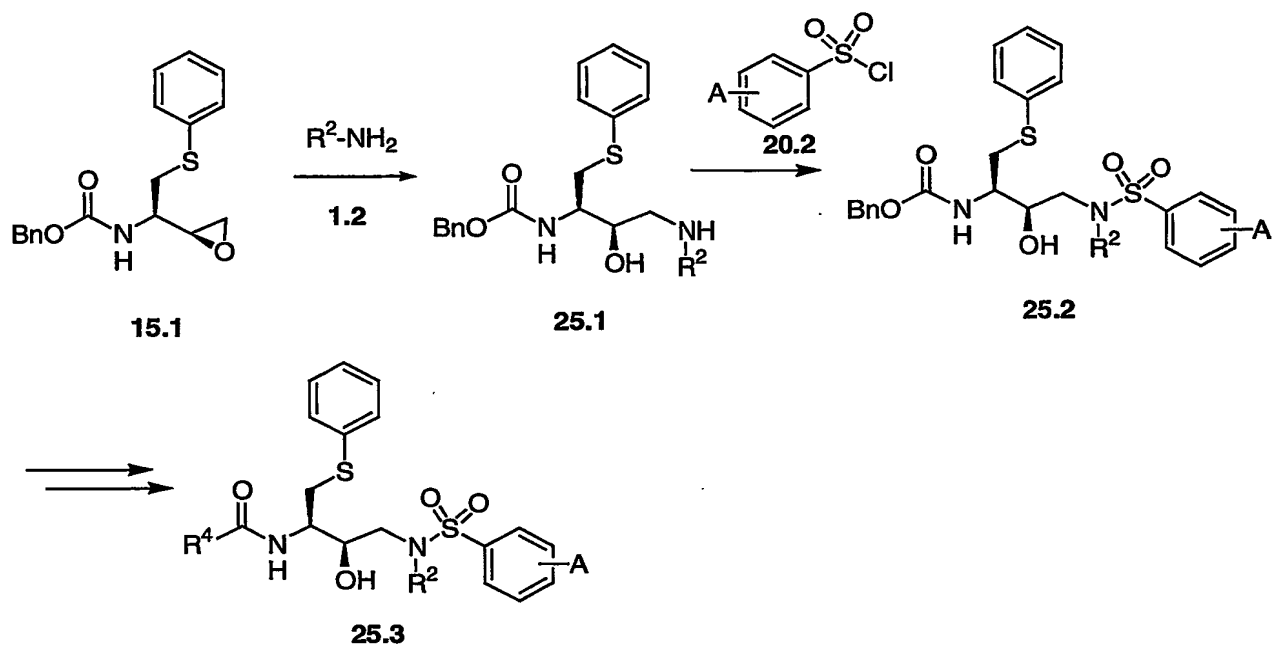
treated with sulfonamide **20.2** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described in Scheme 7, to give the sulfonamide **25.2**. The sulfonamide **25.2** is then converted as described in Scheme 7 for the conversion of **7.9** to **7.10**, and Scheme **9a** for the conversion of **7.10** into **9a.4**, to the product **25.3**. Alternatively, Scheme **26**, illustrates how the amine **8.5** prepared according to Scheme **8** is reacted with **20.2** under conditions described in Scheme **8** for the preparation of **8.6** from **8.5**, to give the sulfonamide **26.1**. Further modification according to the conditions described in Scheme **8** for the preparation of **7.11**, affords sulfonamide **25.3**.

The reactions shown in Scheme **25-26** illustrate the preparation of the compounds sulfonamide **25.3** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **27** depicts the conversion of **25.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **25.3** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.

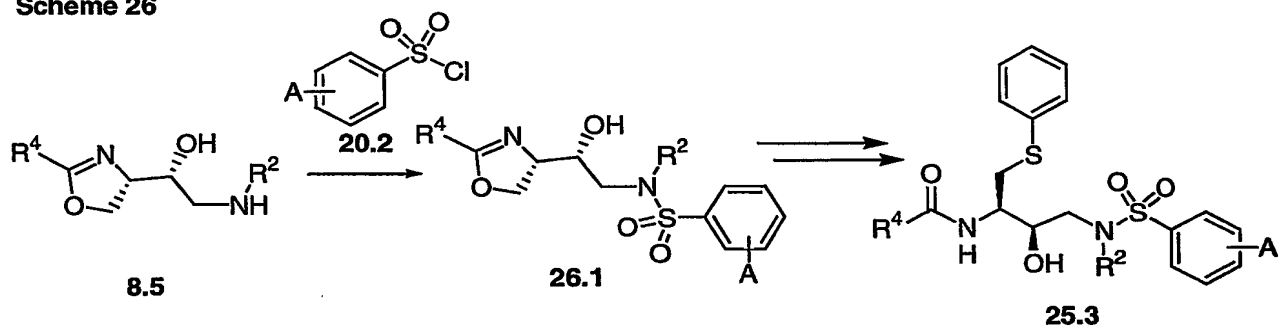
Preparation of the intermediate phosphonate ester **4**, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine are prepared as shown in Schemes **28-29**. Amine **25.2** (Scheme **25**) in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **28.1** as described in Scheme **7** for the preparation of the amine **7.10** from **7.9** and Scheme **9a** for the preparation of **9a.4** from **7.10**.

The reactions shown in Scheme **28** illustrate the preparation of the compounds sulfonamide **28.1** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **29** depicts the conversion of **28.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **28.1** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.

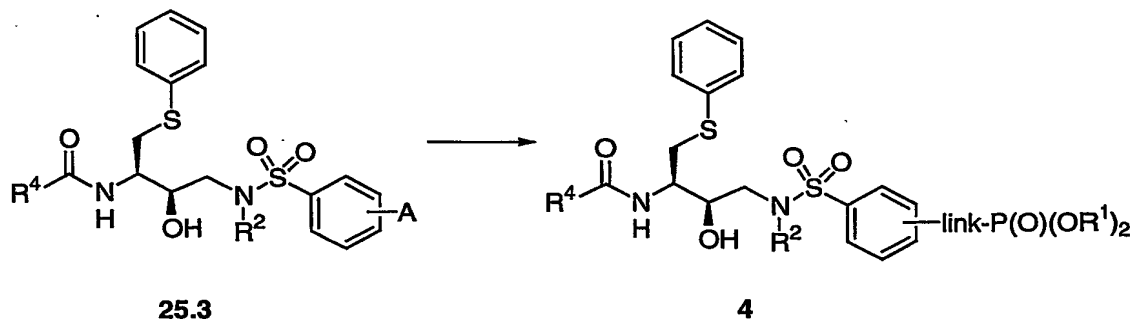
Scheme 25



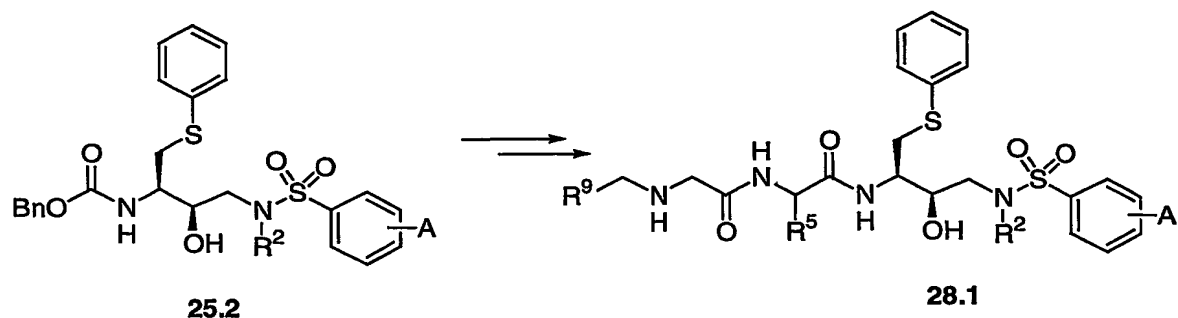
Scheme 26



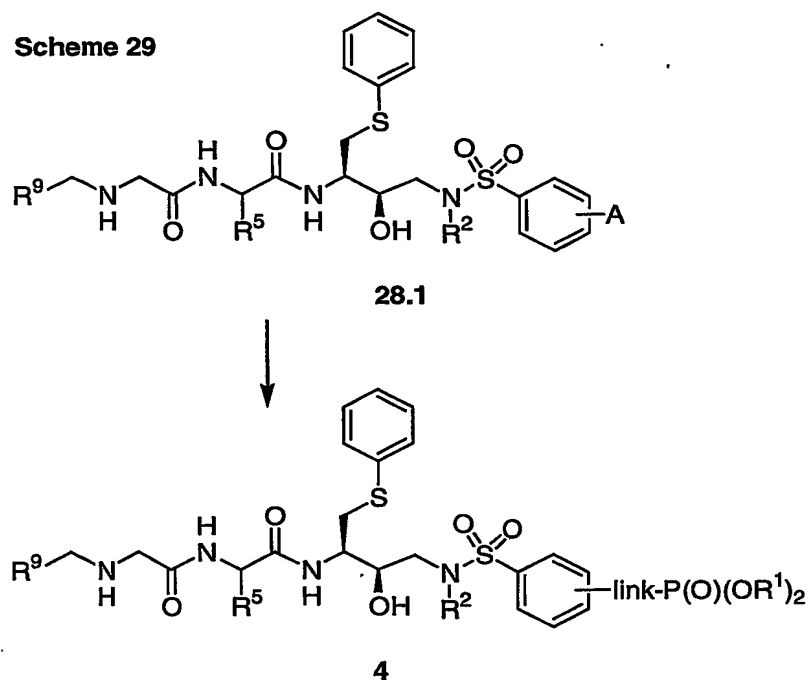
Scheme 27



Scheme 28



Scheme 29



Preparation of the phosphonate ester intermediates 5 in which X is a direct bond

- 5 Schemes 30 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 30, the amine 23.1 (Scheme 23) is reacted with the alcohol 30.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the carbamate 30.2. The reaction is performed under conditions described below, Scheme 98,
- 10 for making carbamates from amines and alcohols. The preparation of the 30.1 is described in

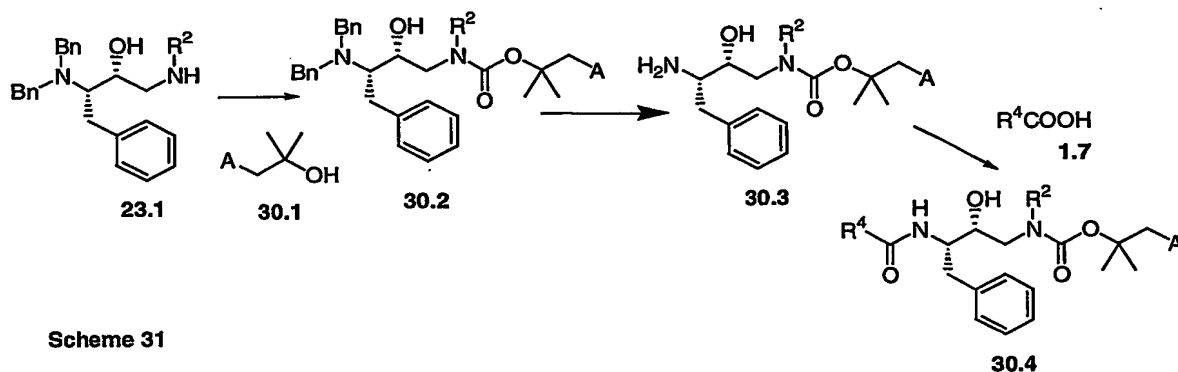
Schemes 83-86. The carbamate **30.2** is then deprotected using conditions described in Scheme 3 for removal of the benzyl groups to give **30.3**. Treatment of **30.3** with the R^4COOH acid **1.7** using the conditions described in Scheme 1 then afford the amide **30.4**

5 The reactions shown in Scheme 30 illustrate the preparation of the compound **30.4** in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 31 depicts the conversion of this compounds **30.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **5** respectively, in which X is a direct bond. In this procedure, the amines **30.4** is converted, using the procedures described below, Schemes
10 **47-99**, into the compounds **5**.

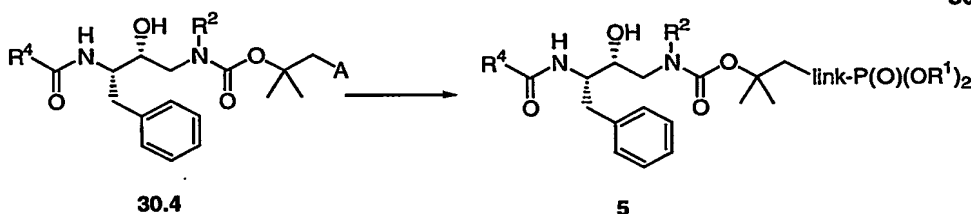
Schemes 32 illustrates the preparation of the phosphonate esters **5** in which X is a direct bond and the R_4COOH group contains an amine. The carbamate **30.2** in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is
15 converted into the chloride **32.1** using conditions as described in Scheme 9a. Chloride **32.1** is then treated with amine **5.7** to give the amine **32.2**, as described in Scheme 9a for the conversion of **7.10** into **9a.3**.

The reactions shown in Scheme 32 illustrate the preparation of the compound **32.2** in which
20 the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 33 depicts the conversion of the compound **32.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **5** in which X is a direct bond. In this procedure, the compound **32.2** is converted, using the procedures described below, Schemes
25 **47-99**, into the compound **5**.

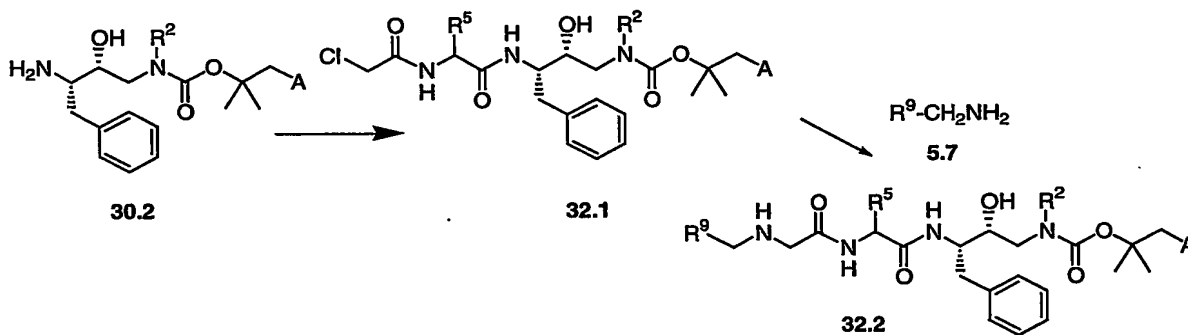
Scheme 30



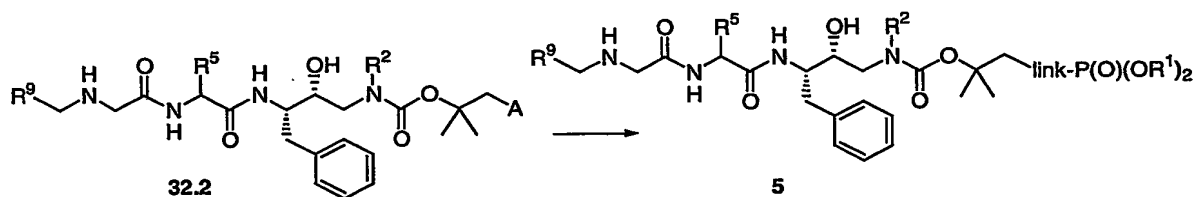
Scheme 31



Scheme 32



Scheme 33



Preparation of the phosphonate ester intermediates 5 in which X is a sulfur

- 5 The intermediate phosphonate ester 5, in which the group A is attached to a sulfur linked aryl moiety, is prepared as shown in Schemes 34-36. Amine 25.1 prepared according to Scheme 25, is treated with alcohol 30.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described below ,

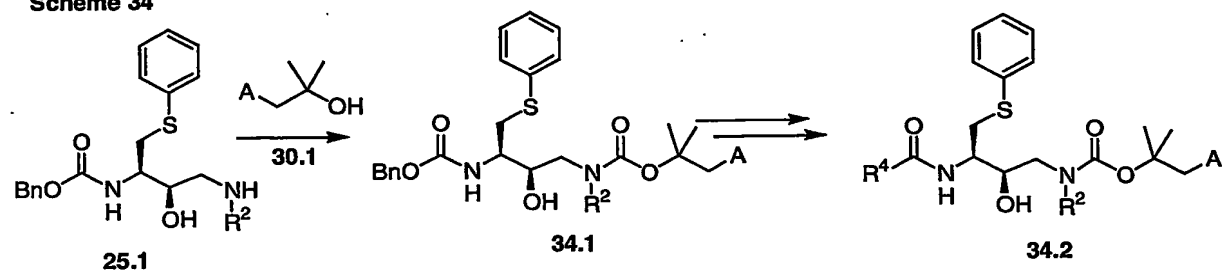
Scheme 98, to give the carbamate **34.1**. The carbamate **34.1** is then converted as described in Scheme 7, for the conversion of **7.9** to **7.11**, to the product **34.2**. Alternatively the amine **8.5** prepared according to Scheme 8 can be reacted with alcohol **30.1** under conditions described in Scheme 98 to give the carbamate **35.1**. Further modification according to the conditions described in Scheme 8, except incorporating thiophenol, then affords sulfonamide **34.2**.

The reactions shown in Scheme 34-35 illustrate the preparation of the compounds sulfonamide **34.2** in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 36 depicts the conversion of **34.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **34.2** is converted, using the procedures described below, Schemes 47-99, into the compound **5**.

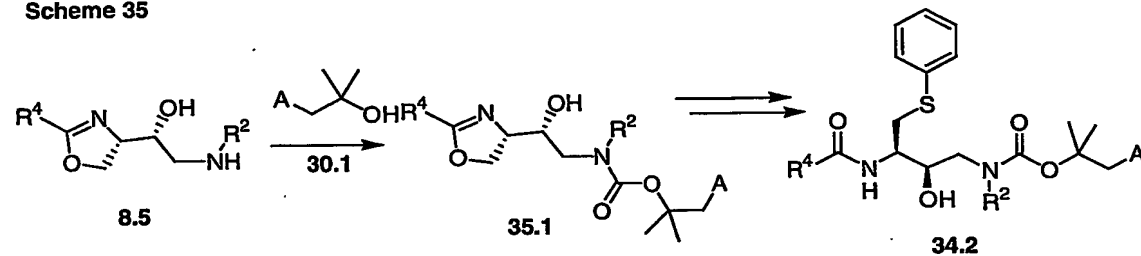
Preparation of the intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains an amine are prepared as shown in Schemes 37-38. Carbamate **34.1** (Scheme 35) in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **37.1**, as described in Scheme 7 for the preparation of the amine **7.10** from **7.9** and Scheme 9a for the preparation of **9a.4** from **7.10**.

The reactions shown in Scheme 37 illustrate the preparation of the compounds sulfonamide **37.1** in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 38 depicts the conversion of **37.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **37.1** is converted, using the procedures described below, Schemes 47-99, into the compound **5**.

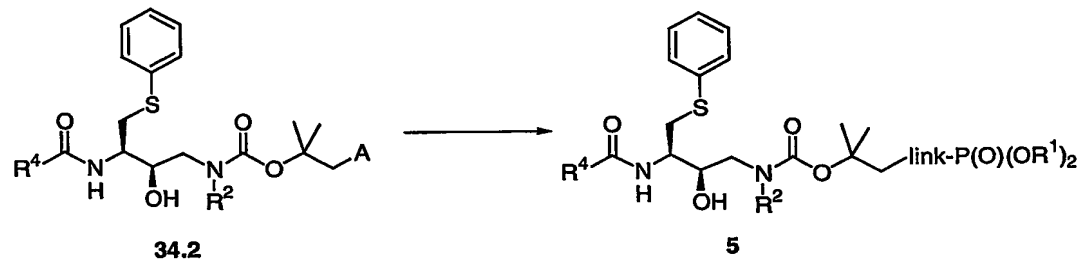
Scheme 34



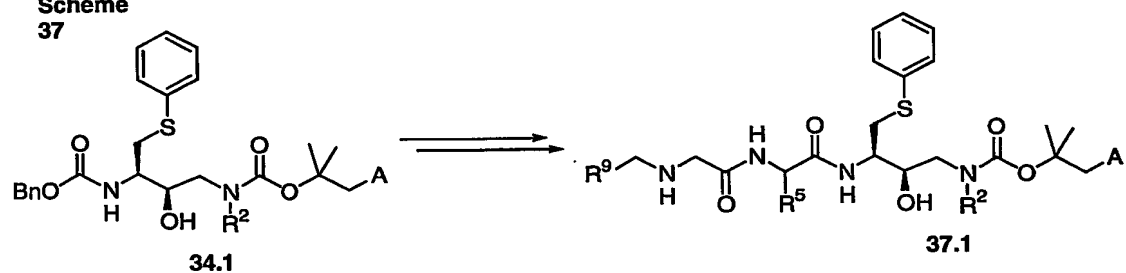
Scheme 35



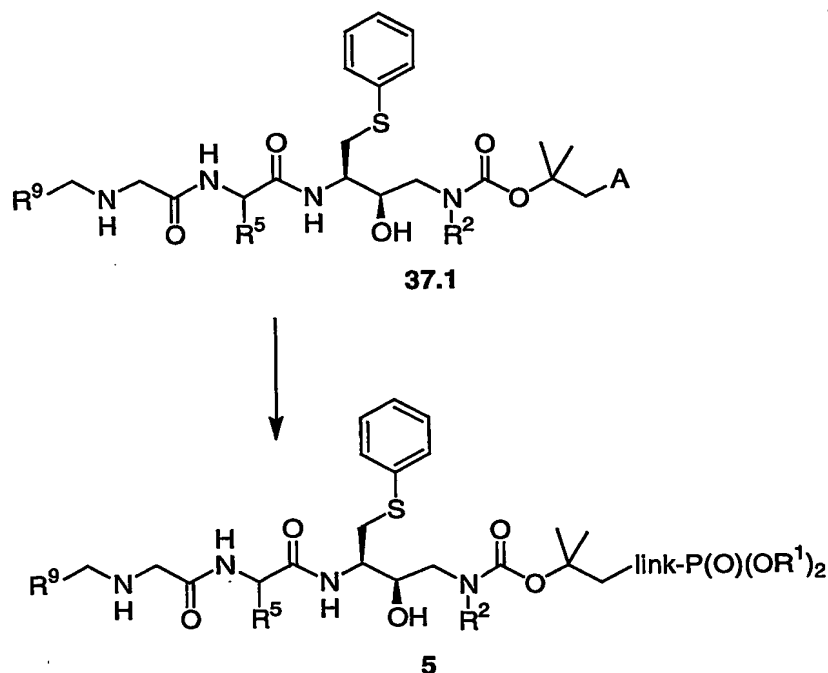
Scheme 36



Scheme 37



Scheme 38

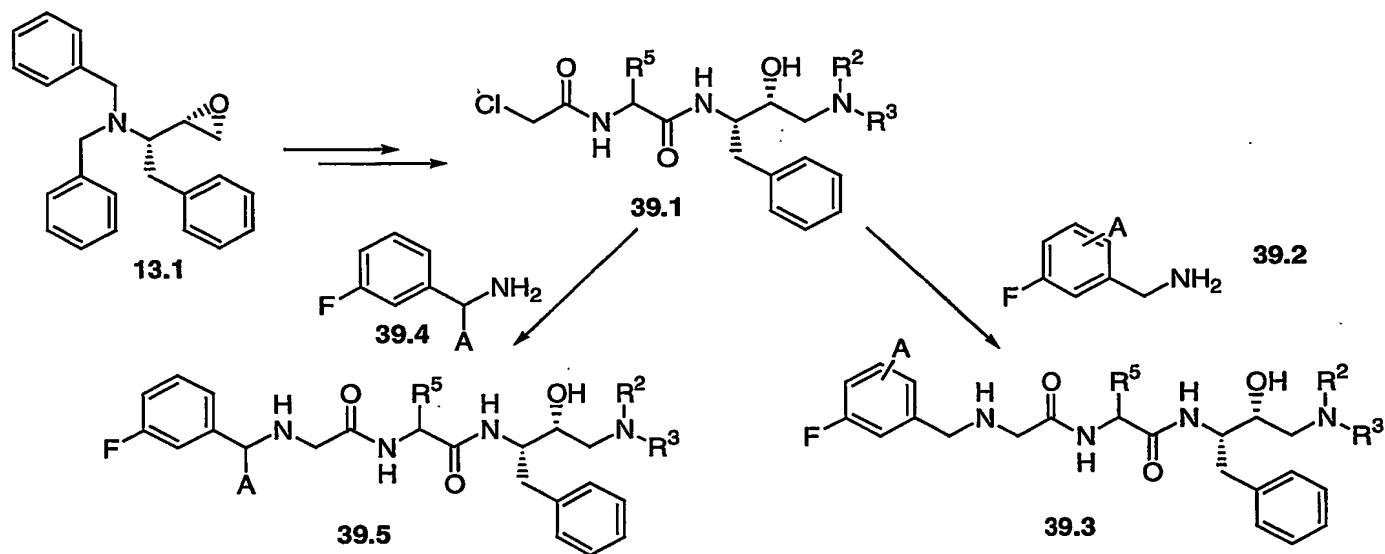


Preparation of the phosphonate ester intermediates 6 and 7 in which X is a direct bond

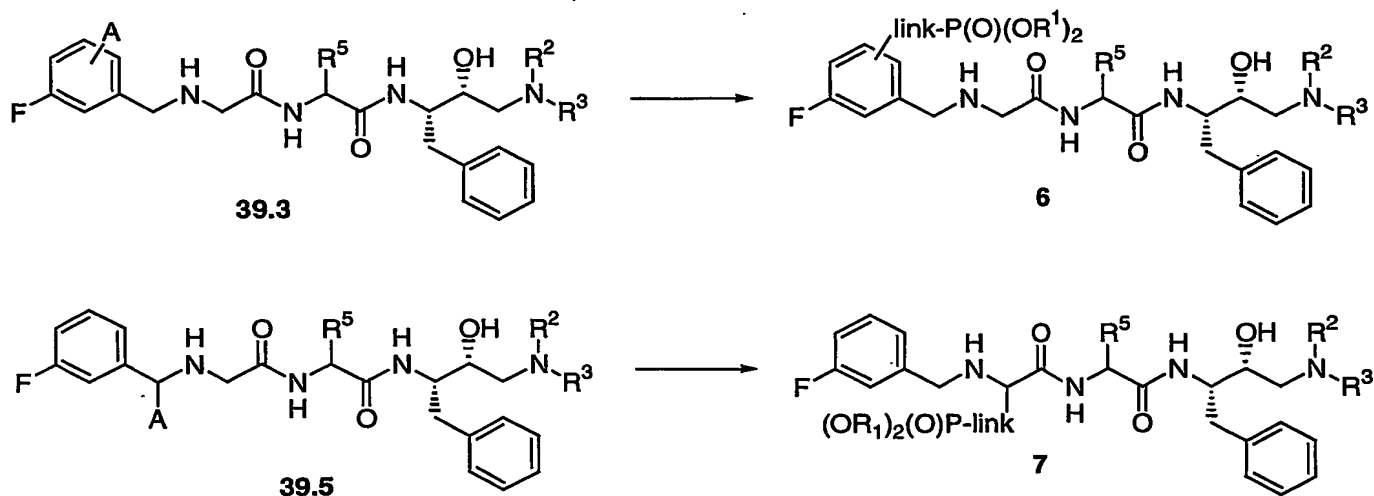
- 5 Schemes 39-40 illustrate the preparation of the phosphonate esters 6 and 7 in which X is a direct bond. As shown in Scheme 39, the epoxide 13.1, prepared as described in Scheme 13 is converted to the chloride 39.1, as described in Scheme 3, for the preparation of 3.4, and Scheme 5, for the conversion of 3.4 into 5.6. The chloride 39.1 is then reacted with the amine 39.2 or 39.4, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor
- 10 such as [OH], [SH], [NH], Br etc, to afford the amine 39.3 and 39.5 respectively. The reaction is performed under the same conditions as described above, Scheme 5 for the preparation of the amine 5.8 from 5.6. The preparation of 39.2 and 39.4, amines in which A is link-P(O)(OR¹)₂, are shown in Schemes 79-80 and Schemes 81-82 respectively.
- 15 The reactions shown in Scheme 39 illustrate the preparation of the compounds 39.3 and 39.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 40 depicts the conversion of these compounds 39.3 and 39.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 6 and 7 respectively, in

which X is a direct bond. In this procedure, the amines **39.3** and **39.5** are converted, using the procedures described below, Schemes 47-99, into the compounds **6** and **7** respectively.

Scheme 39



Scheme 40



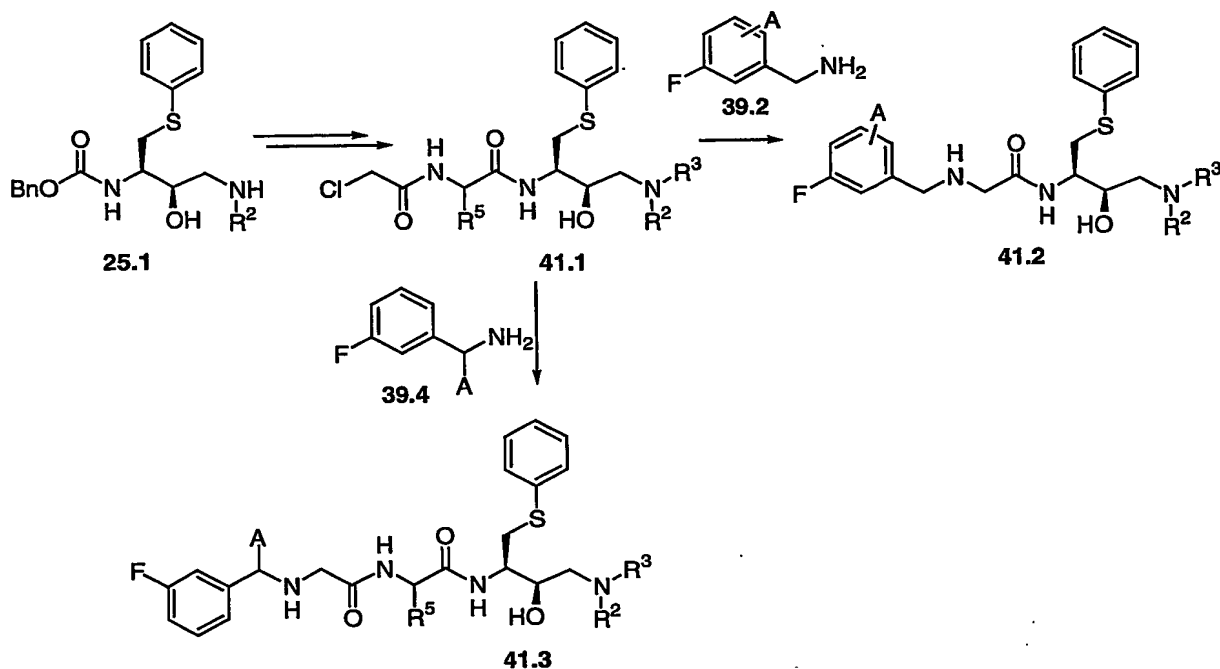
Preparation of the phosphonate ester intermediates **6** and **7** in which X is a sulfur

The intermediate phosphonate esters **6** and **7**, in which the group **A** is attached to a sulfur linked aryl moiety, are prepared as shown in Scheme 41-42. The amine **25.1** (Scheme 25) is

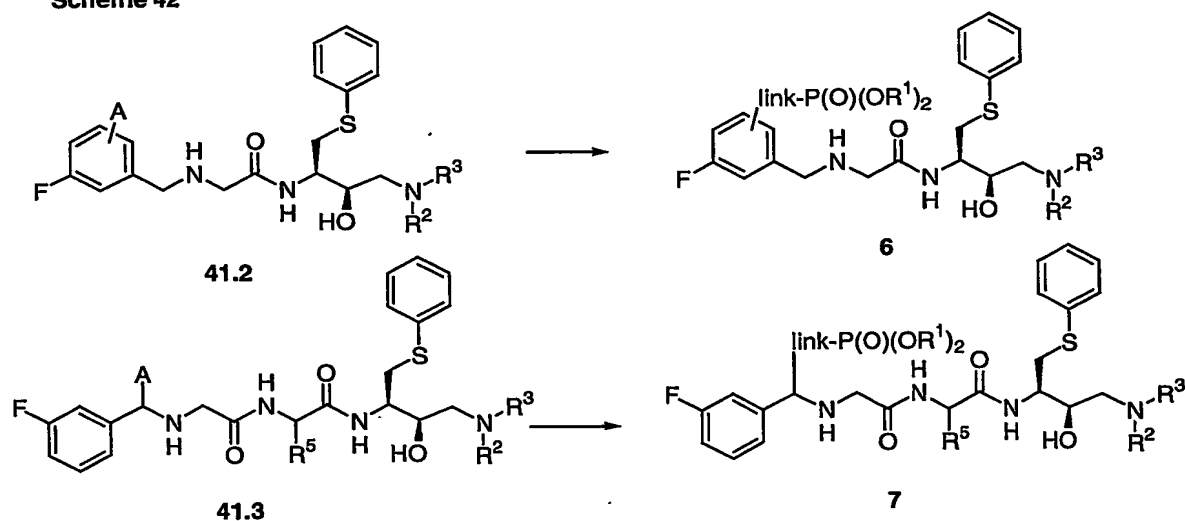
converted to the chloride **41.1** as described in Scheme 7 for the preparation of **7.10** from **7.8**, and Scheme 9a for conversion of **7.10** to **9a3**. The chloride **41.1** is then treated with amine **39.2** or amine **39.4**, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 5, to give the amines **41.2** and **41.3** respectively.

The reactions shown in Scheme 41 illustrate the preparation of the compounds **41.2** and **41.3** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 42 depicts the conversion of **41.2** and **41.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **6** and **7** in which X is sulfur. In this procedure **41.2** or **41.3** is converted, using the procedures described below, Schemes 47-99, into the compound **6** and **7**.

Scheme 41



Scheme 42



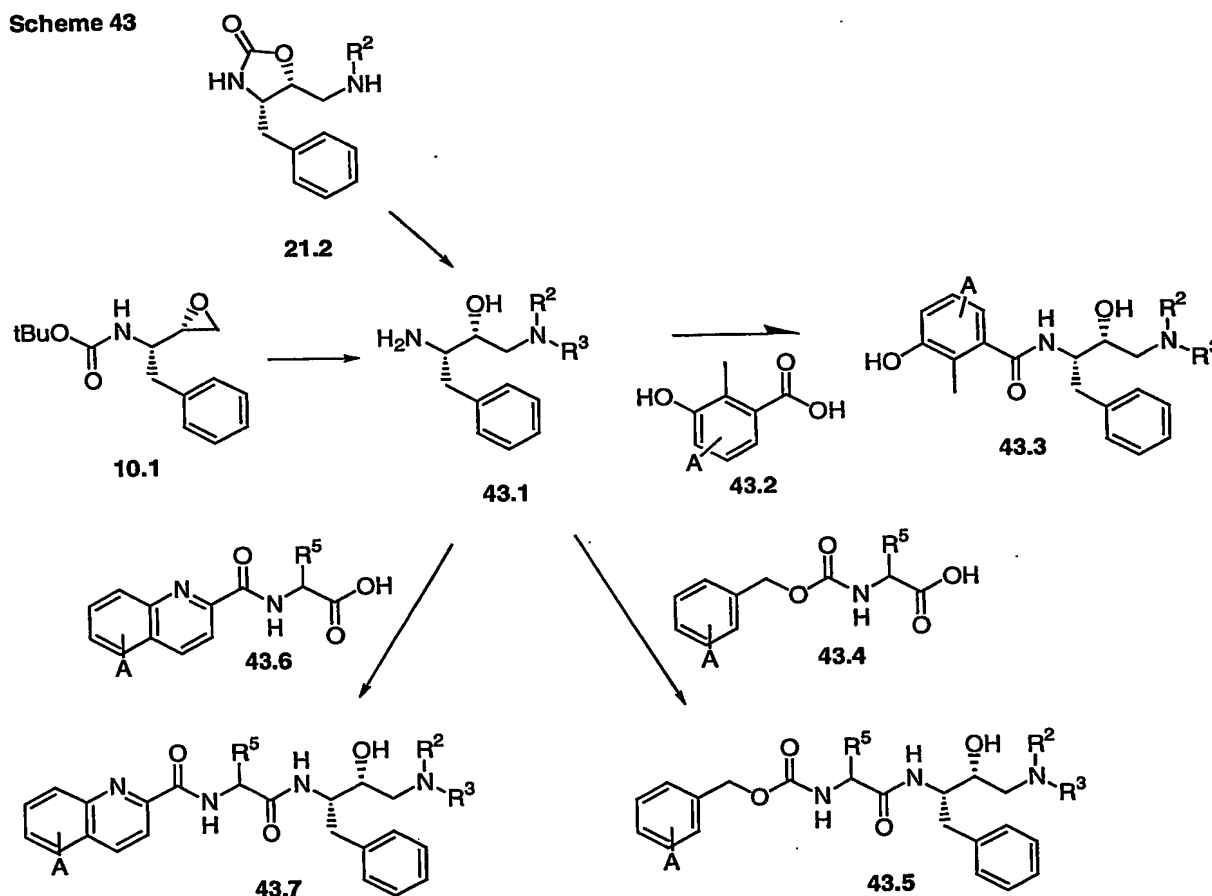
Preparation of the phosphonate ester intermediates 8-10 in which X is a direct bond

- 5 Schemes 43-44 illustrate the preparation of the phosphonate esters 8-10 in which X is a direct bond. As shown in Scheme 43, the amine 43.1 prepared from 10.1 or 21.2 is reacted with the acid 43.2, 43.4 or 43.6, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amide 43.3, 43.5 and 43.7 respectively. The reaction is performed under the same conditions as described above, Scheme

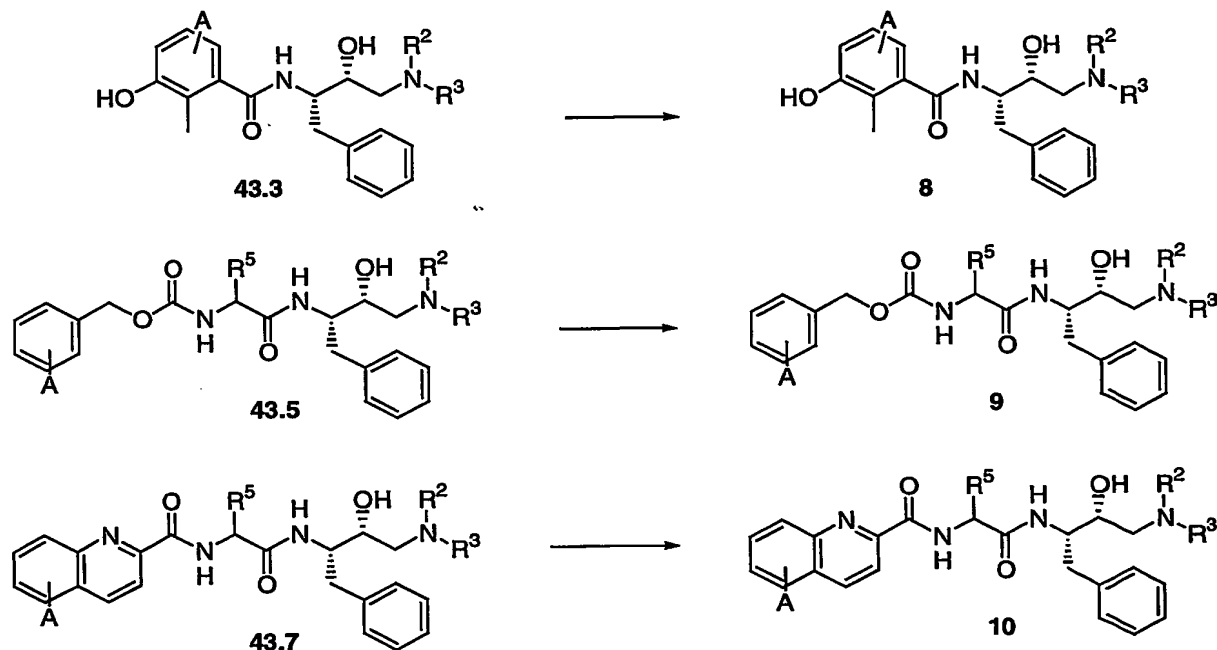
1 for the preparation of the amide 1.8. Amine 43.1 is prepared from epoxide 10.1 using the conditions described in Scheme 1 except utilising 10.1 in place of 1.1. Amine 43.1 is prepared from 21.2 according to the conditions described in Scheme 2 except utilizing 21.2 in place of 2.1. The preparation of the acid 43.2 is described in Schemes 47-51, acid 43.4 is described in Schemes 87-91, and acid 43.6 is described in Schemes 52-55.

The reactions shown in Scheme 43 illustrate the preparation of the compounds 43.3, 43.5 and 43.7 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 44 depicts the conversion of these compounds 43.3, 43.5, and 43.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 8, 9 and 10 respectively, in which X is a direct bond. In this procedure, the amines 43.3, 43.5 and 43.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9, and 10 respectively.

Scheme 43



Scheme 44



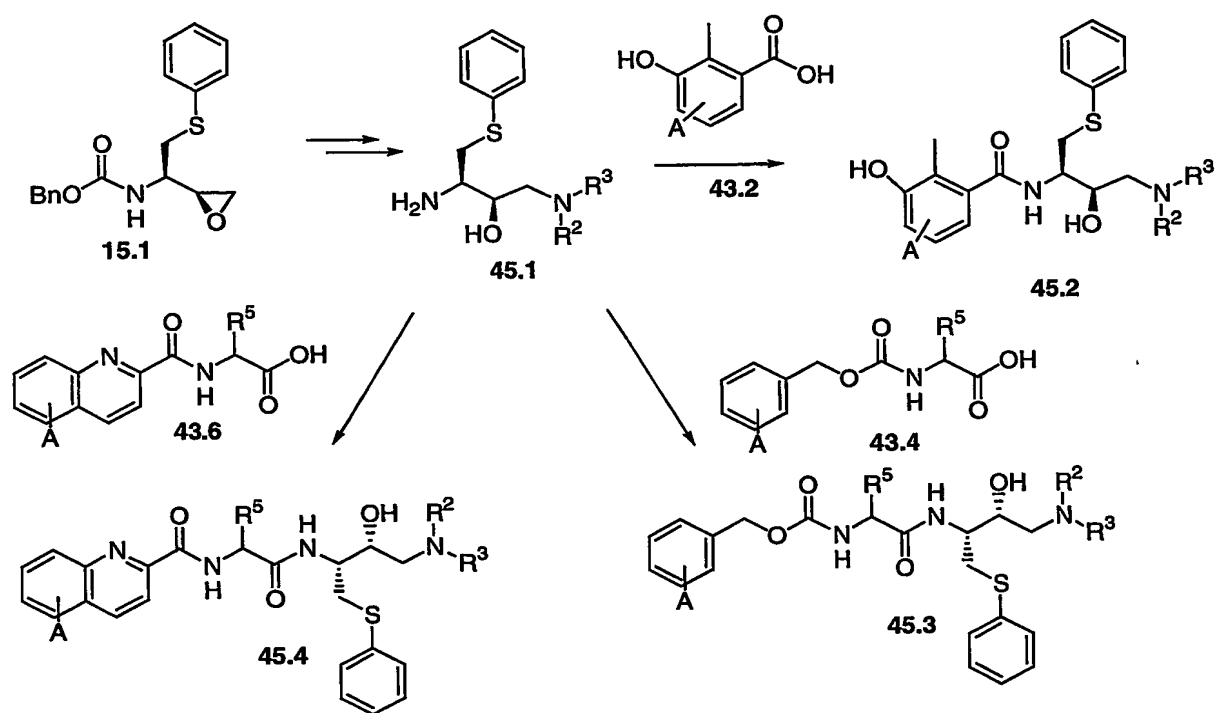
Preparation of the phosphonate ester intermediates 8-10 in which X is a sulfur

- 5 The intermediate phosphonate esters 8-10, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Schemes 45-46. In Scheme 45, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 except incorporating thiophenol for thiol 7.2. The epoxide 15.1 is then converted to amine 45.1 according to the conditions described in Scheme 7 for the preparation of 7.10 from 7.7. Amine 45.1 is then
- 10 treated with acids 43.2, 43.4 or 43.6, in which substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amides 45.2, 45.3, and 45.4 respectively.

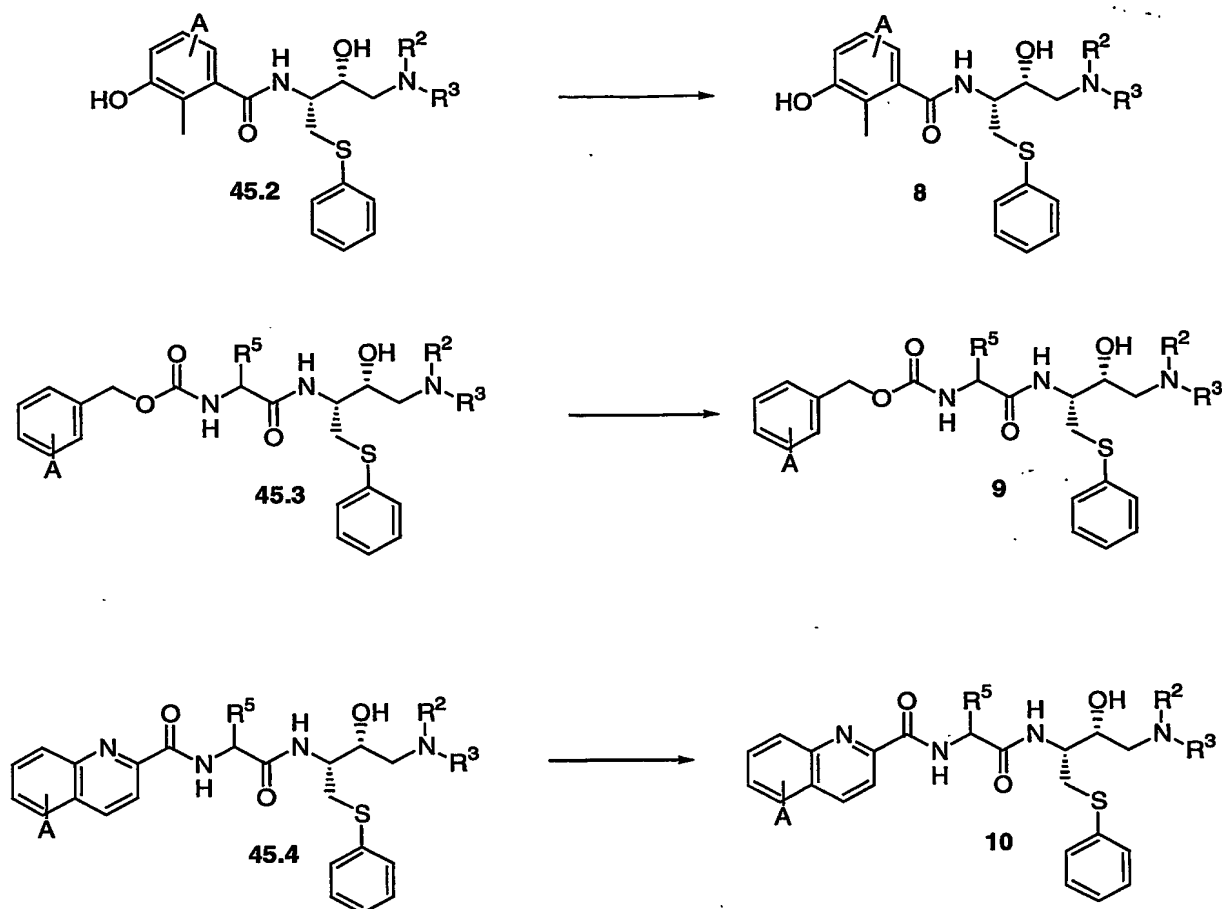
The reactions shown in Scheme 45 illustrate the preparation of the compounds 45.2, 45.3, and

15 45.4 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 46 depicts the conversion 45.2, 45.3, and 45.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 8, 9 and 10 respectively in which X is sulfur. In this procedure 45.2, 45.3, and 45.4 is converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9 and 10 respectively.

Scheme 45



Scheme 46



Preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2.

- 5 Schemes 47 - 51 illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2 which are employed in the preparation of the phosphonate esters 8.

10 Scheme 47 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 47.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 47.2. This compound is reacted with a chlorodialkyl phosphite 47.3 to yield the phenylphosphonate ester 47.4, which upon deprotection affords the carboxylic acid 47.5.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **47.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **47.7**, as described in

- 5 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **47.8**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **47.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **47.10**. Halogen-metal exchange is performed by the
- 10 reaction of the substrate **47.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **47.3**, to produce the phosphonate **47.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **47.12**.
- 15 Using the above procedures, but employing, in place of the bromo compound **47.6**, different bromo compounds **47.1**, there are obtained the corresponding products **47.5**.

Scheme 48 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

- 20 In this method, a suitably protected dimethyl hydroxybenzoic acid, **48.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **48.2** is reacted with a sodium dialkyl phosphite, **48.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **48.4**. Deprotection of the carboxyl function then yields the carboxylic acid **48.5**.
- 25 For example, 2,5-dimethyl-3-hydroxybenzoic acid, **48.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **48.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or
- 30 diisopropylethylamine. The product **48.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **48.8**. This compound is then reacted with a sodium dialkyl

phosphite **48.3** in tetrahydrofuran, as described above, to afford the phosphonate **48.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **48.10**. Using the above procedures, but employing, in place of the methyl compound **48.6**, different methyl compounds **48.1**, there are obtained the corresponding products **48.5**.

Scheme **49** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic acid **49.1** is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **49.2**, to afford the coupled product **49.3**, which upon deprotection affords the carboxylic acid **49.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **49.5**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **49.6**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether **49.7**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **49.2**, under the conditions of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product **49.8**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **49.9**.

Using the above procedures, but employing, in place of the phenol **49.5**, different phenols or thiophenols **49.1**, there are obtained the corresponding products **49.4**.

Scheme 50 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 50.2 is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 50.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product 50.3 is deprotected to afford the phosphonate 50.4; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid 50.5.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 50.6, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester 50.7 as described above. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 50.8, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, using the conditions described above to afford the product 50.9. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products 50.10 and 50.11.

Using the above procedures, but employing, in place of the bromo compound 50.6, different bromo compounds 50.1, and/or different phosphonates 50.2, there are obtained the corresponding products 50.4 and 50.5.

Scheme 51 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 51.1 is converted to the corresponding boronic acid 51.2, by metallation with butyllithium and boronation, as described in *J. Organomet. Chem.*, 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 51.3. The product 51.4 is then deprotected to afford the diaryl phosphonate product 51.5.

For example, the silylated OBO ester **51.6**, prepared as described above, (Scheme 47), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp.

Radiopharm., 1992, 31, 175, is converted into the boronic acid **51.7**, as described above. This

material is coupled with a dialkyl 4-bromophenyl phosphonate **51.8**, prepared as described in

5 J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as

catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium

reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **51.9**.

Deprotection, as described above, then affords the benzoic acid **51.10**.

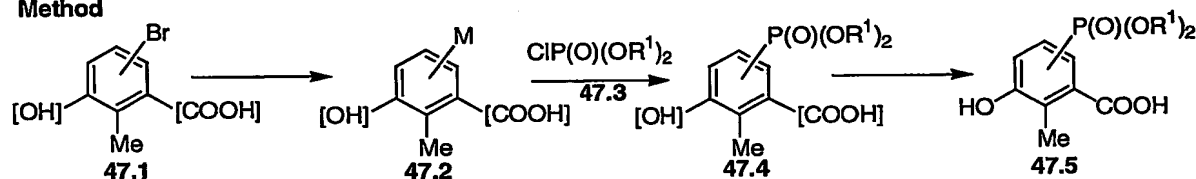
Using the above procedures, but employing, in place of the bromo compound **51.6**, different

10 bromo compounds **51.1**, and/or different phosphonates **51.3**, there are obtained the

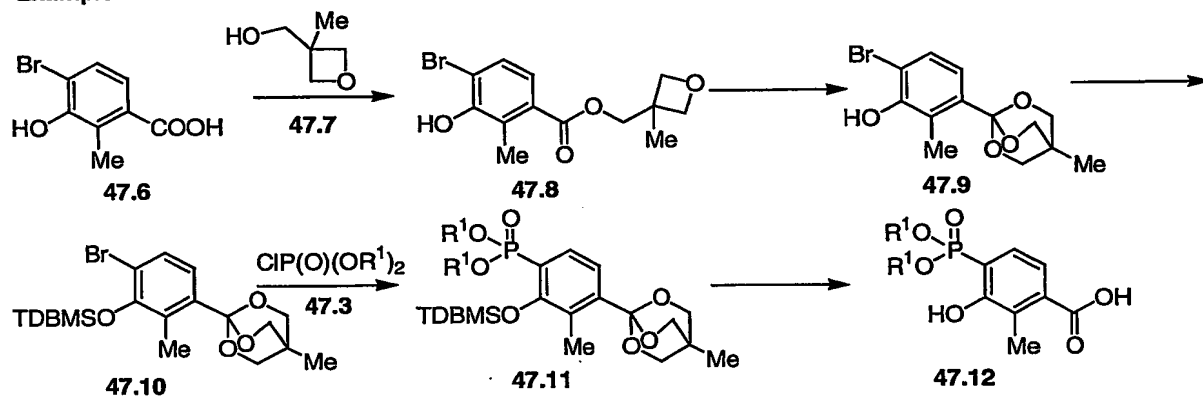
corresponding carboxylic acid products **51.5**.

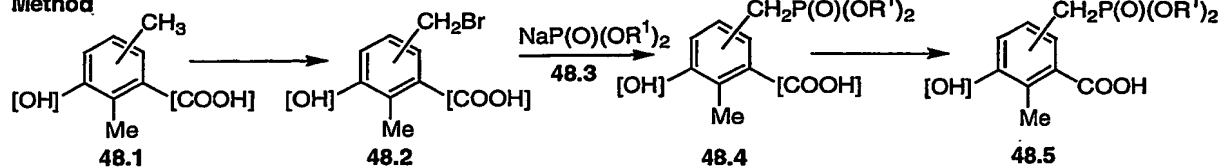
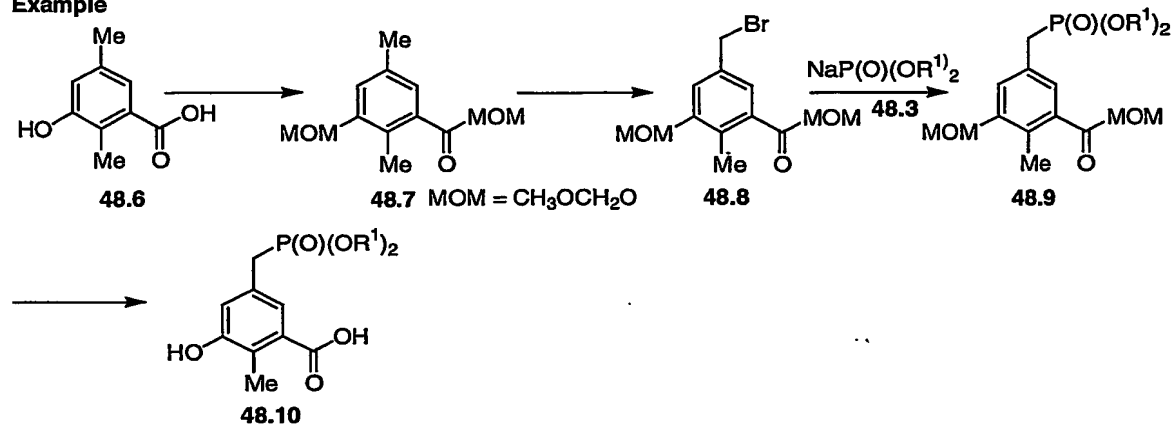
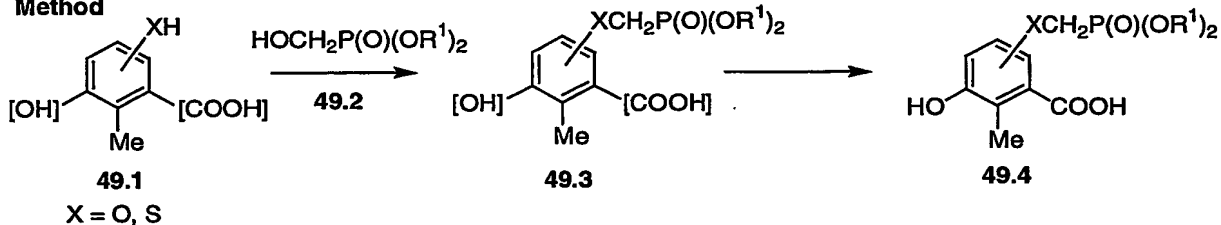
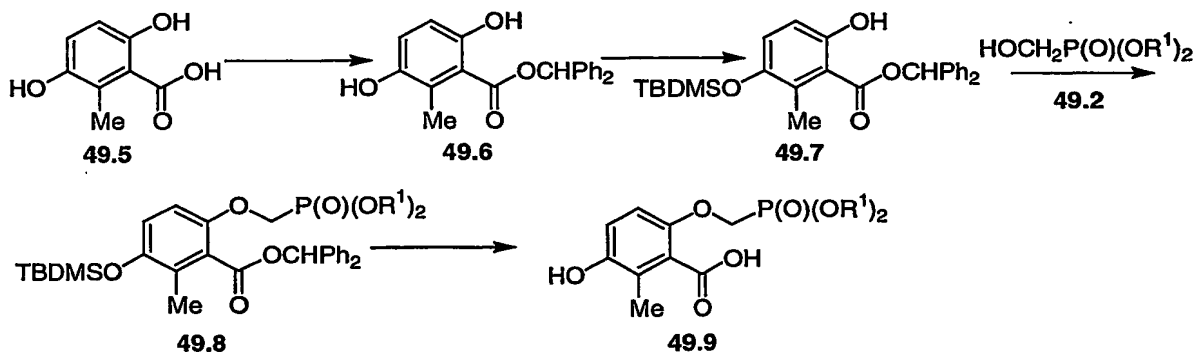
Scheme 47

Method

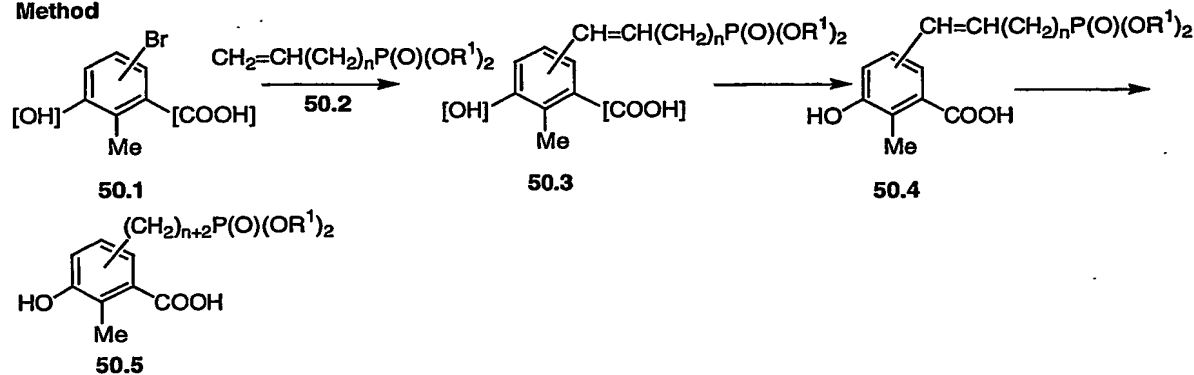


Example

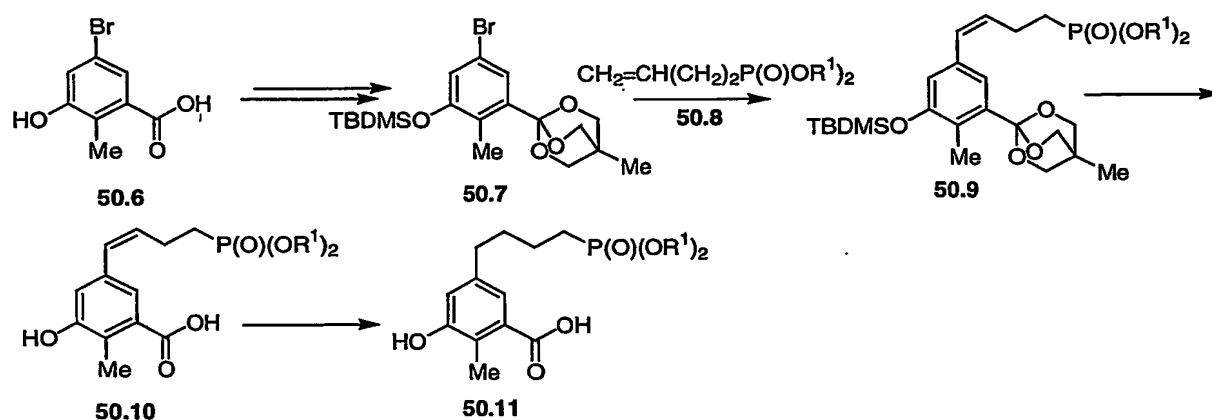


Scheme 48**Method****Example****Scheme 49****Method****Example**

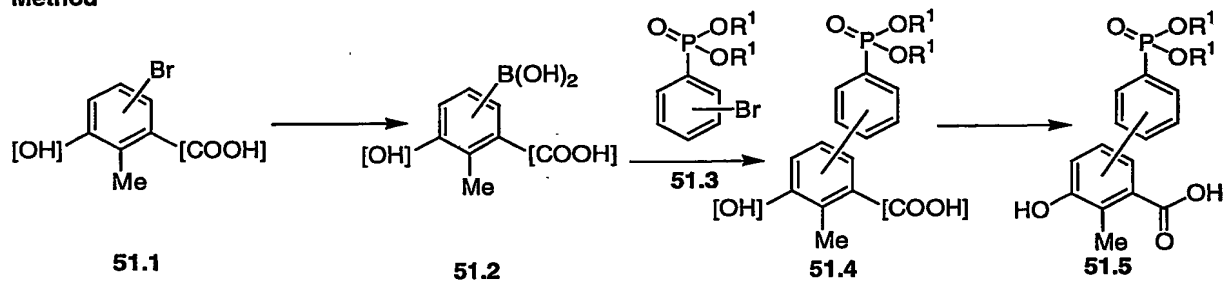
Scheme 50
Method



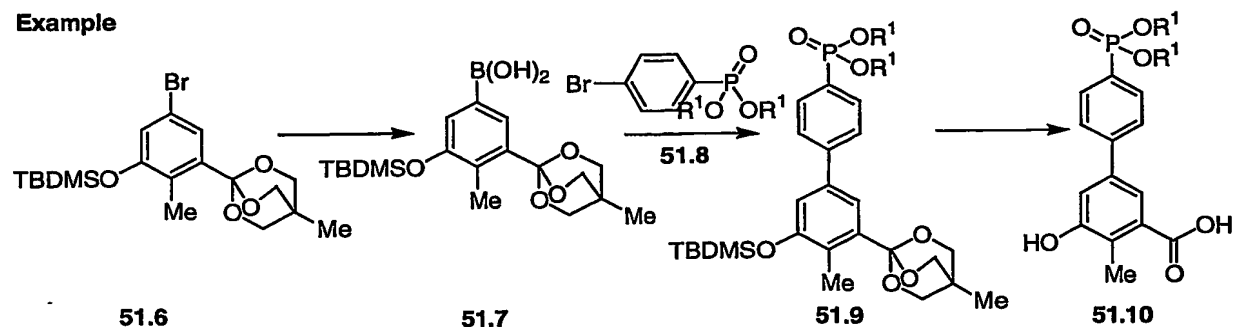
Example



Scheme 51
Method



Example



Preparation of quinoline 2-carboxylic acids 43.6 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes 43 - 46 for the preparation of the phosphonate esters 10 employ a quinoline-2-carboxylic acid reactant 43.6 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme 52 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 52.1 is reacted with an alkyl pyruvate ester 52.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 52.3. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid 52.4. The carboxylic acid product 52.4 in which X is NH₂ can be further transformed into the corresponding compounds 52.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **52.6**, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **52.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **52.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **52.3** instead of the carboxylic acids **52.5**.

For example, 2,4-diaminobenzaldehyde **52.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **52.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **52.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **52.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **52.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **52.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **52.11**, Z = Br. Alternatively, the diazonium tetrafluoborate **52.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **52.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **52.7**, different aminobenzaldehydes **52.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **52.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes 53 – 55) into phosphonate-containing derivatives.

Scheme 53 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **53.1** is transformed, via a diazotization procedure as described above (Scheme 52) into the corresponding phenol or

thiol **53.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **53.3**, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester **53.4**. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **53.4**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **53.5**. The product is then coupled with a suitably protected aminoacid derivative **53.6** to afford the amide **53.7**. The reaction is performed under similar conditions to those described above, Scheme 1. The ester protecting group is then removed to yield the carboxylic acid **53.8**.

For example, methyl 6-amino-2-quinoline carboxylate **53.9**, prepared as described in *J. Het. Chem.*, 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **53.10**. This material is reacted with a dialkyl hydroxymethylphosphonate **53.11** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **53.12**. Basic hydrolysis then afford the carboxylic acid **53.13**. The latter compound is then converted, as described above, into the aminoacid derivative **53.16**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **53.9**, different aminoquinoline carboxylic esters **53.1**, and/or different dialkyl hydroxymethylphosphonates **53.3** the corresponding phosphonate ester products **53.8** are obtained.

Scheme 54 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **54.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **54.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

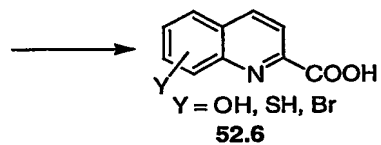
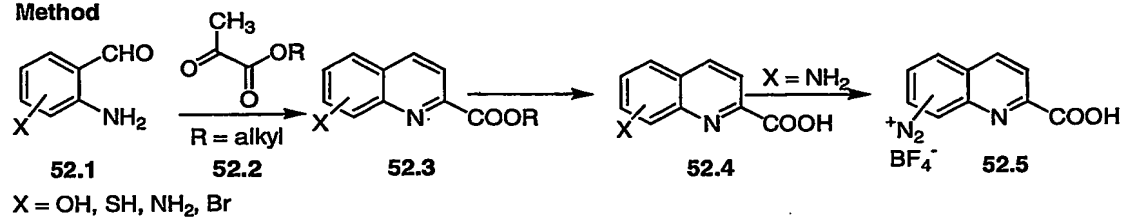
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **54.1** and the olefin **54.2** affords the olefinic ester **54.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **54.4**. The latter compound is then transformed, as described above, into the homolog **54.5**. Optionally, the unsaturated carboxylic acid **54.4** can be reduced to afford the saturated analog **54.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product **54.6** is then converted, as described above (Scheme 53) into the aminoacid derivative **54.7**.

For example, methyl 7-bromoquinoline-2-carboxylate, **54.8**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate **54.9** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **54.10**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **54.11**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **54.12**. The latter compound is then converted, as described above, into the aminoacid derivative **54.13**. The unsaturated product **54.11** is similarly converted into the analog **54.14**.

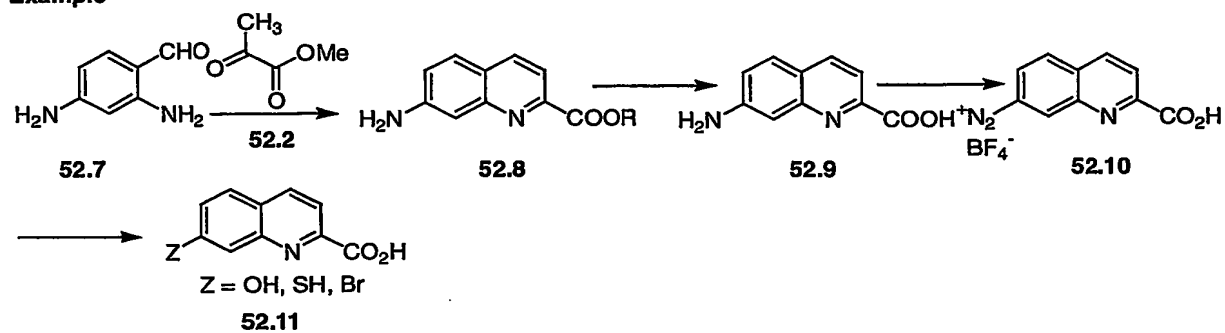
Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **54.8**, different bromoquinoline carboxylic esters **54.1**, and/or different dialkyl alkenylphosphonates **54.2**, the corresponding phosphonate ester products **54.5** and **54.7** are obtained.

Scheme 52

Method

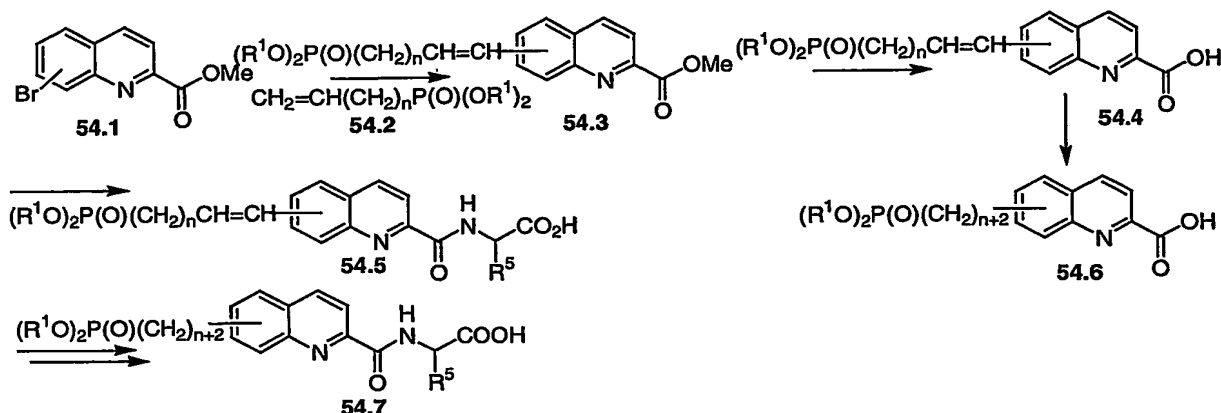


Example

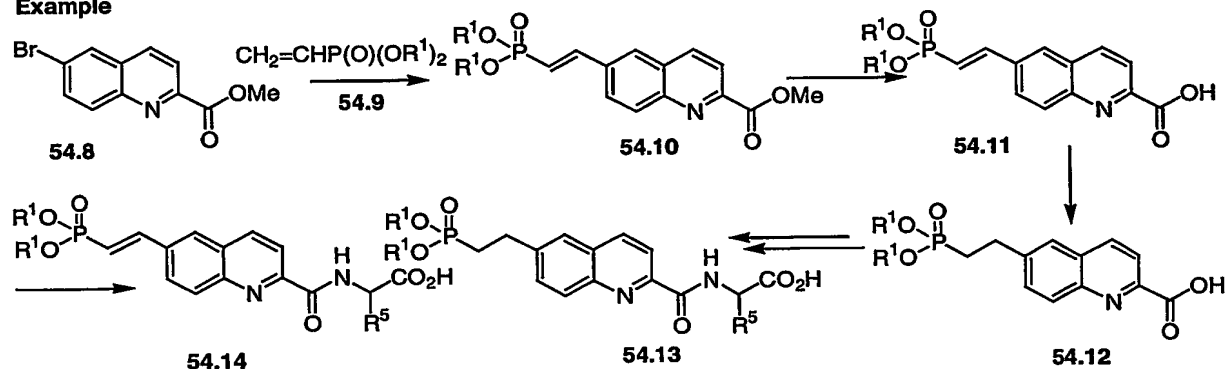


Scheme 54

Method

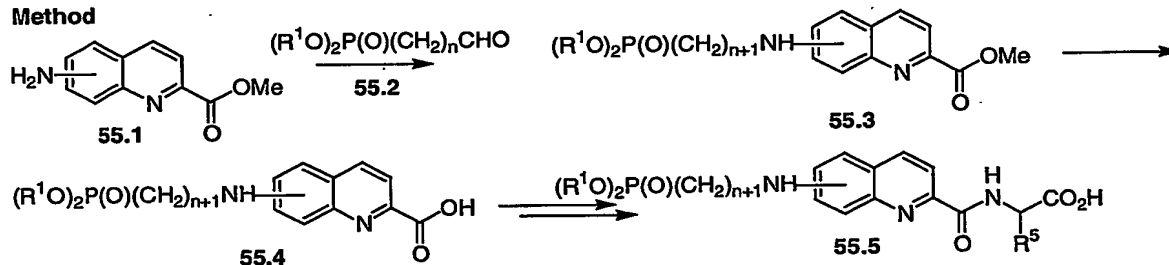
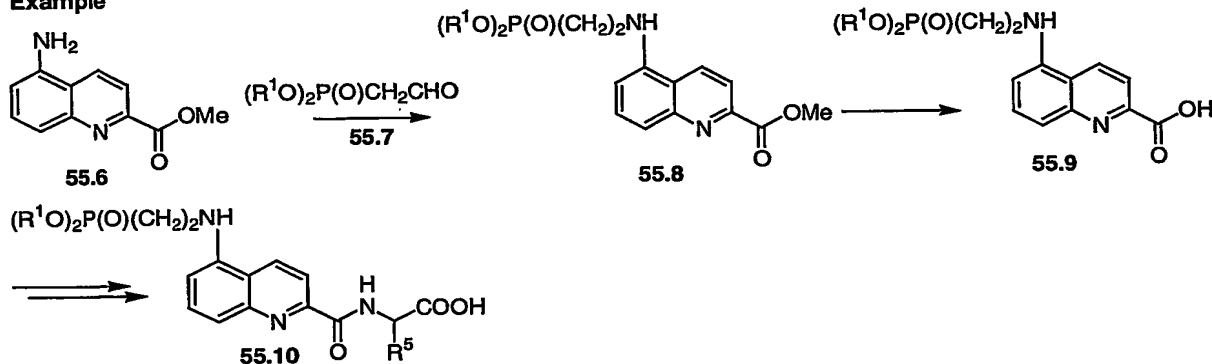


Example



Scheme 55 depicts the preparation of quinoline-2-carboxylic acid derivatives 55.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 55.1 is reacted with a phosphonate aldehyde 55.2 under reductive amination conditions, to afford the aminoalkyl product 55.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 55.3 is then hydrolyzed to yield the free carboxylic acid 55.4. The latter compound is then converted, as described above, into the amino acid derivative 55.5.

For example, methyl 7-aminoquinoline-2-carboxylate **55.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **55.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **55.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **55.9**. The latter compound is then converted, as described above, into the aminoacid derivative **55.10**.
 5 Using the above procedures, but employing, in place of the formylmethyl phosphonate **55.7**, different formylalkyl phosphonates **55.2**, and/or different aminoquinolines **55.1**, the corresponding products **55.5** are obtained.

Scheme 55**Method****Example**

10

Preparation of phenylalanine derivatives 1.1 incorporating phosphonate moieties.

Scheme **56** illustrates the conversion of variously substituted phenylalanine derivatives **56.1**
 15 into epoxides **1.1**, the incorporation of which into the compounds **1** is depicted in Schemes **1** and **3**.

A number of compounds **56.1** or **56.2**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds **56.1** or **56.2** are described in the literature. For example, the preparation of compounds **56.1** or **56.2** in which

X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Am. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds **56.1**, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids **56.2** are protected, for example by conversion to the BOC derivative **56.3**, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product **56.3** is then converted into the methyl ester **56.4**, for example by treatment with ethereal diazomethane. The substituent X in **56.4** is then transformed, using the methods described below, Schemes **57-59**, into the group A. The products **56.5** are then converted, via the intermediates **56.6 - 56.9**, into the epoxides **1.1**. The methyl ester **56.5** is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid **56.6**. The conversion of the carboxylic acid **56.6** into the epoxide **1.1**, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **56.7**. The diazoketone is converted into the chloroketone **56.8** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **56.9** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**. Optionally, the above described series of reactions can be performed on the methyl ester **56.4**, so as to yield the epoxide **1.1** in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds **56.4**, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes **57-59**.

Scheme **56a** illustrates the conversion of variously substituted phenylalanine derivatives **56a.1** into epoxides **3.1**, the incorporation of which into the compounds **1** is depicted in Schemes **3**. Starting from the same reagents described above, Scheme **56**, the compound **56.2** is converted

into the epoxide **56a.6** as described in J. Org. Chem 1996,61, 3635. The amino acid **56.2** is converted to the tribenzyl ester **56a.3** by treatment with benzyl bromide in ethanol in the presence of potassium carbonate. The substituent X in **56a.3** is then transformed, using the methods described below, Schemes **57-59**, into the group A, compound **56a.4**. These methods describe procedures in which the amine is BOC protected. However the same procedures are applicable to other amine protecting groups such as dibenzyl. The products **56a.4** are then converted, via the intermediates **56a.5** into the epoxides **3.1**. The ester **56a.4** is reduced with lithium aluminum hydride to the alcohol which is then oxidized to the aldehyde **56a.4** by treatment with pyridine sulfur trioxide in DMSO and triethylamine. The aldehyde **56a.4** is then converted to the epoxide **3.1** by treatment with chloromethylbromide and excess lithium in THF at -65°C . A mixture of isomers are produced which are separated by chromatography.

Scheme **57** depicts the preparation of epoxides **57.4** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **57.1** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **57.2**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH_2 or NHalkyl , an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH_2OH , a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **57.3**, which, employing the sequence of reactions shown in Scheme **56** or **56a**, is transformed into the epoxide **57.4**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **57.5** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **57.6**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60° , to afford the ether product **57.5**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **57.8**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **57.1** in place of **57.5**, and/or different phosphonates **57.2**, the corresponding products **57.4** are obtained.

Scheme 58 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 58.1 is reacted with a dialkyl bromoalkyl phosphonate 58.2 to afford the product 58.3. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a suitable base such as sodium hydride or cesium carbonate. The product is then transformed, using the sequence of reactions shown in Scheme 56, into the epoxide 58.4.

For example, the protected aminoacid 58.5, prepared as described above (Scheme 56) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate 58.6, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 58.7. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide 58.8.

Using the above procedures, but employing different phenols, thiols, and amines 58.1 in place of 58.5, and/or different phosphonates 58.2, the corresponding products 58.4 are obtained.

Scheme 59 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

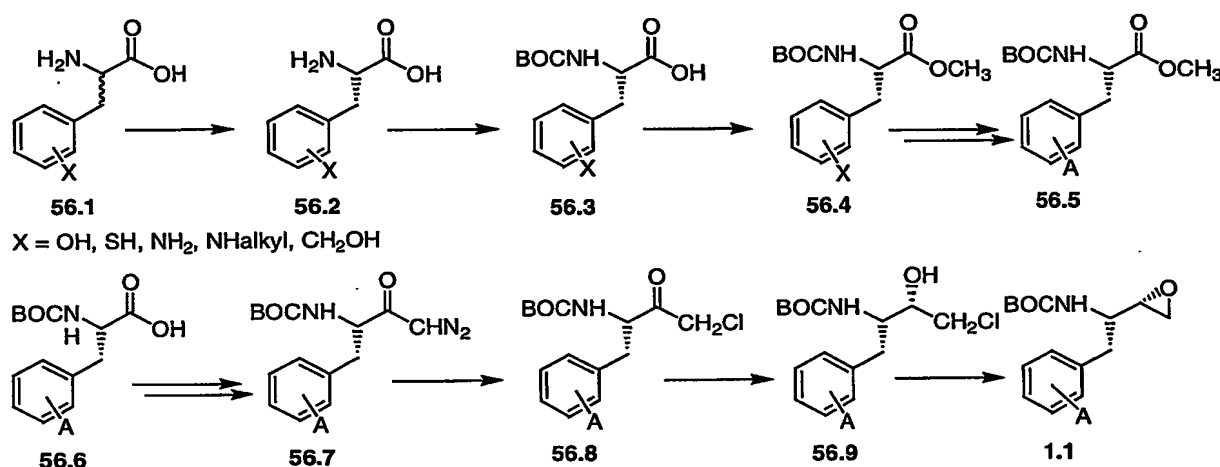
In this procedure, a protected hydroxymethyl-substituted phenylalanine 59.1 is converted into the halomethyl-substituted compound 59.2. For example, the carbinol 59.1 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 108, 1035, 1986 to afford the product 59.2 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 59.3. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 59.4, which, employing the sequence of reactions shown in Scheme 56, is transformed into the epoxide 59.5.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 59.6, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in

Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **59.7**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **59.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **59.9**. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide **59.10**.

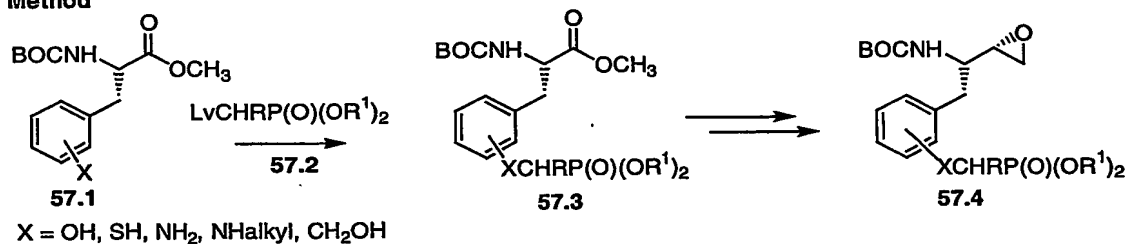
Using the above procedures, but employing different carbinols **59.1** in place of **59.6**, and/or different phosphonates **59.3**, the corresponding products **59.5** are obtained.

Scheme 56

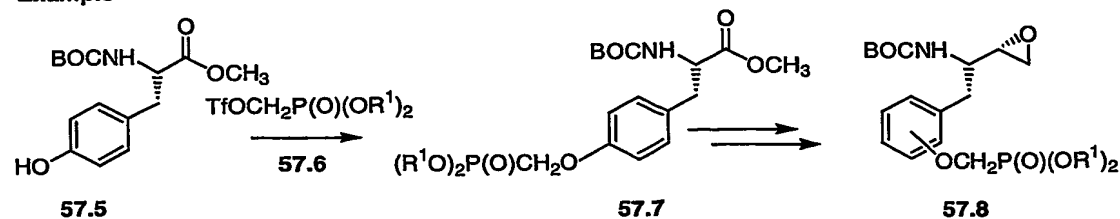


Scheme 57

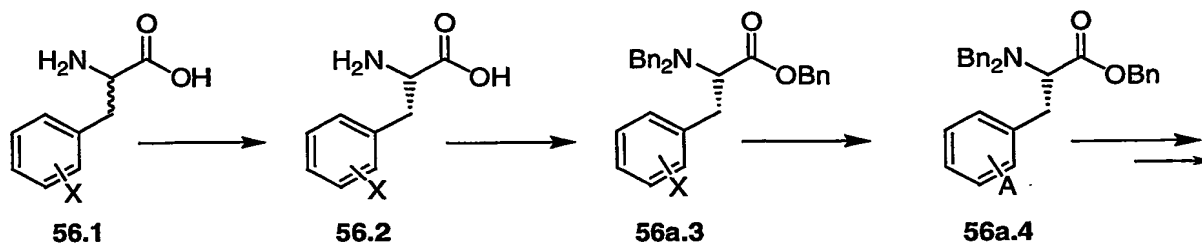
Method



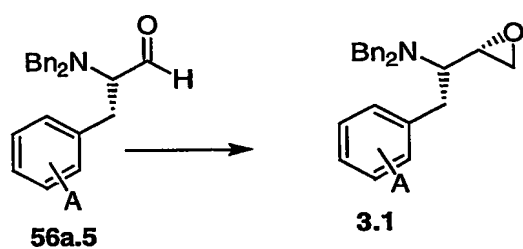
Example



Scheme 56a

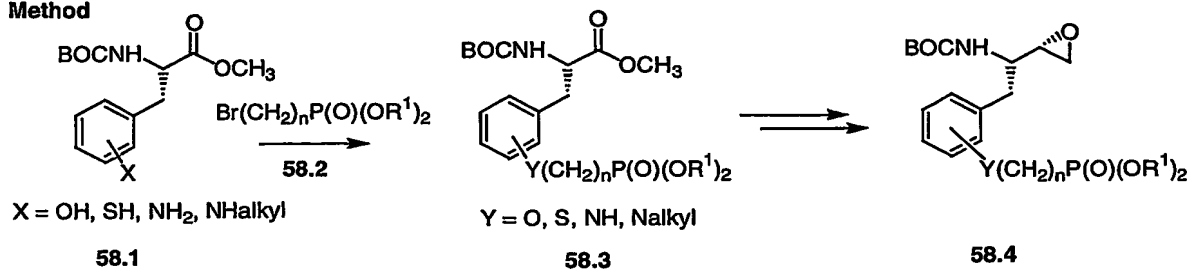


X = OH, SH, NH_2 , NHalkyl, CH_2OH

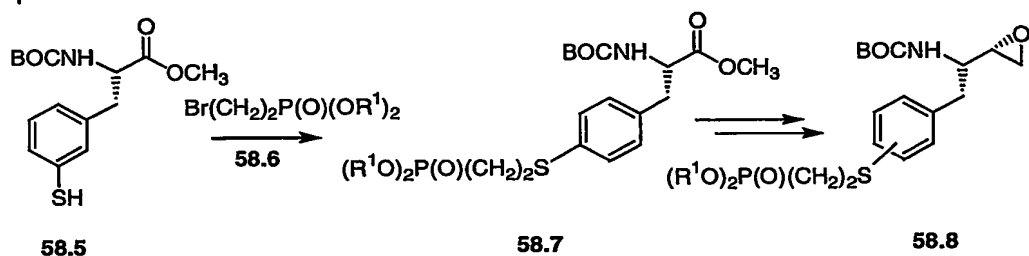


Scheme 58

Method

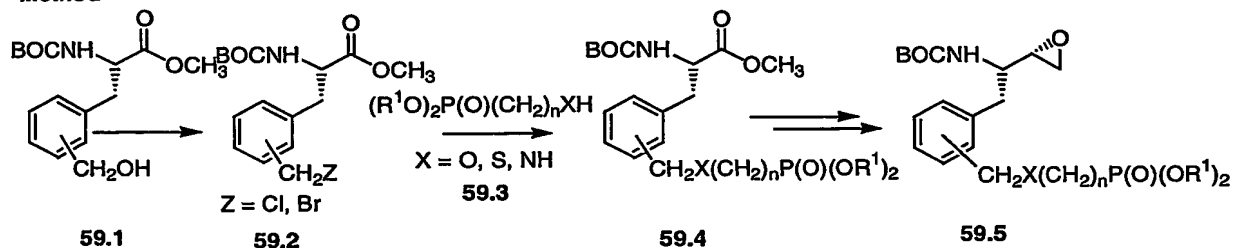


Example

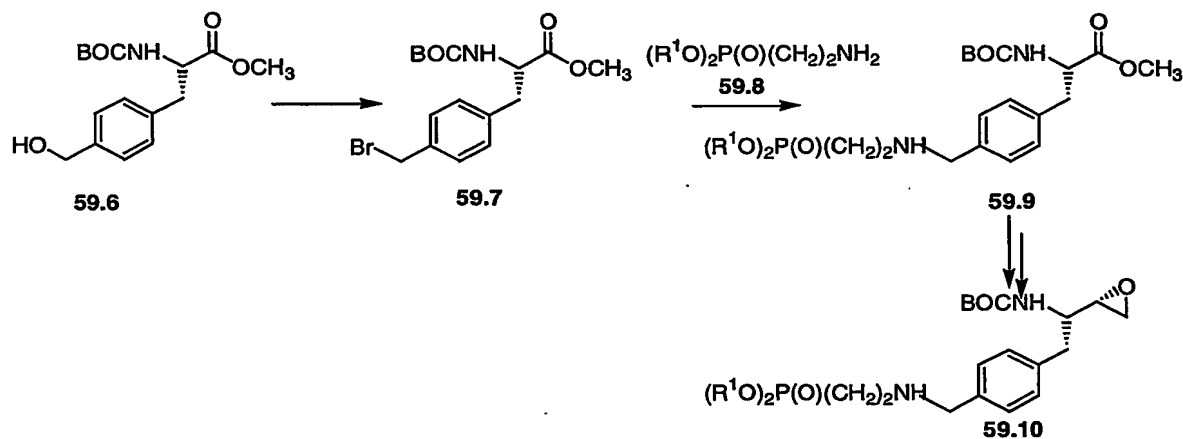


Scheme 59

Method



Example



Preparation of phenylalanine derivatives 2.1 incorporating phosphonate moieties or precursors thereto.

Scheme 60 illustrates the preparation of the hydroxymethyl oxazolidine derivative **2.1**, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this reaction sequence, the substituted phenylalanine **60.1**, in which A is as defined above, is transformed, via the intermediates **60.2** - **60.9**, into the hydroxymethyl product **2.1**. In this procedure, phenylalanine, or a substituted derivative thereof, **60.1**, is converted into the phthalimido derivative **60.2**. The conversion of amines into phthalimido derivatives is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **60.2**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **60.3**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **60.3**, X = Cl, is then converted into the aldehyde **60.4** by means of a reduction reaction. This procedure is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride **60.3** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde **60.4**. The aldehyde **60.4** is then transformed into the cyanohydrin derivative **60.5**. The conversion of aldehydes into cyanohydrins is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde **60.4** is converted into the cyanohydrin **60.5** by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described

in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **60.6**. The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **60.5** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **60.6**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **60.7**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **60.7**. For example, the aminoacid **60.6** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **60.7**. The latter compound is then transformed into the oxazolidinone **60.8**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester **60.9** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **60.8** is converted into the methyl ester **60.9** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **60.9** is then reduced to yield the corresponding carbinol **2.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **60.9** is reduced to the carbinol **2.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

The conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **2.1** has been incorporated into

the intermediates **1**. Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **2.1** are shown below, (Schemes **61-62**)

Scheme **61** depicts the preparation of hydroxymethyl oxazolidinones **61.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **61.1** is converted, using the series of reactions illustrated in Scheme **60**, into the bromophenyl oxazolidinone **61.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **61.3**, to afford the phosphonate product **61.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **61.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **61.5**, using the procedure described above (Scheme **60**)

For example, 3-bromophenylalanine **61.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **60**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **61.7**. This compound is then coupled with a dialkyl phosphite **61.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **61.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **61.9**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **61.6** different bromophenylalanines **61.1** and/or different dialkyl phosphites **61.3**, the corresponding products **61.5** are obtained.

Scheme **62** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **62.9** and **62.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **62.1** is converted into the benzyl ester **62.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in

5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester **62.3** is then reacted

10 with phthalic anhydride, as described above (Scheme **60**) to afford the phthalimide **62.4**. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **62.5**. This compound is transformed, by means of the series of reactions shown in Scheme **60**, into the carbomethoxy oxazolidinone **62.6**, using in each step the same conditions as are described above (Scheme **60**). The protected OH or

15 SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into

20 the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **62.7** is then reacted with a hydroxyalkyl phosphonate **62.20** under the conditions of the Mitsunobu reaction, as described above (Scheme **49**), to afford the ether or thioether **62.8**. The latter compound is then reduced with sodium borohydride, as described

25 above (Scheme **60**) to afford the hydroxymethyl analog **62.9**. Alternatively, the phenol or thiophenol **62.7** is reacted with a dialkyl bromoalkyl phosphonate **62.10** to afford the alkylation product **62.11**. The alkylation reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium

30 carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **62.12**.

For example, 3-hydroxyphenylalanine **62.13** (Fluka) is converted in to the benzyl ester **62.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **62.15**. The protected ether is then reacted with phthalic anhydride, as described above
5 (Scheme 60) to yield the phthalimido-protected compound **62.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **62.17**. This compound is then transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy-substituted oxazolidinone **62.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient
10 temperature, to produce the phenol **62.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **62.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and
15 R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction yields the phenolic ether **62.21**. The carbomethoxy group is then
20 reduced by reaction with sodium borohydride, as described above, to afford the carbinol **62.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **62.13**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl hydroxyalkyl phosphonates **62.20**, the corresponding products **62.9** are obtained.

25 As a further example of the methods illustrated in Scheme 62, 4-mercaptophenylalanine **62.23**, prepared as described in J. Am. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **62.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm.
30 Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **62.27**. The latter compound is then transformed, by means of the series of reactions

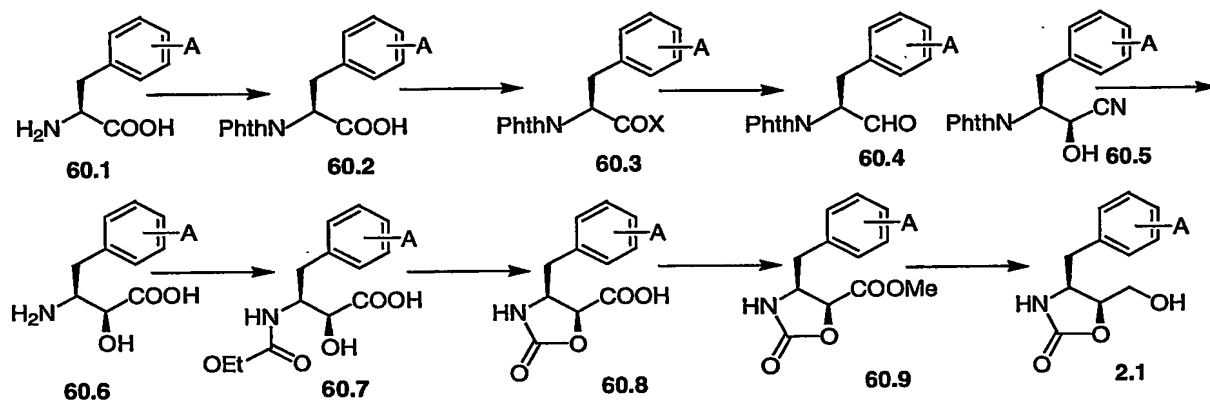
shown in Scheme 60, into the carbomethoxy oxazolidinone **62.28**. The adamantyl protecting group is then removed by treatment of the thioether **62.28** with mercuric acetate in trifluoroacetic acid at 0°, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol **62.29**. The thiol is then reacted with one molar equivalent of a dialkyl

5 bromoethylphosphonate **62.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°, to afford the thioether product **62.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **62.32**.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine **62.23**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl

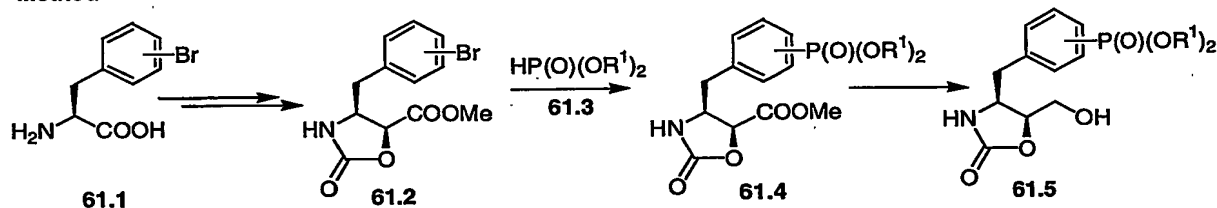
10 bromoalkyl phosphonates **62.10**, the corresponding products **62.12** are obtained.

Scheme 60

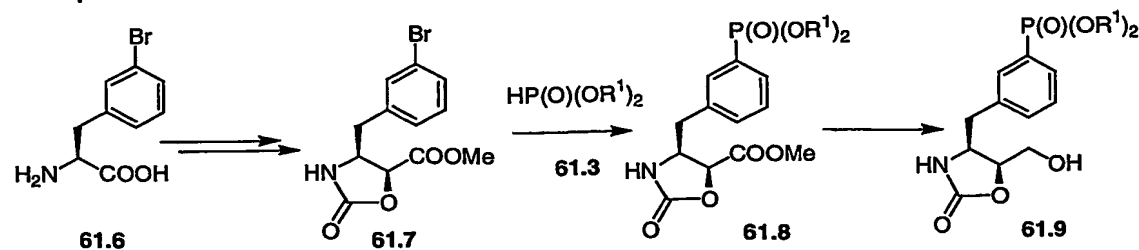


Scheme 61

Method

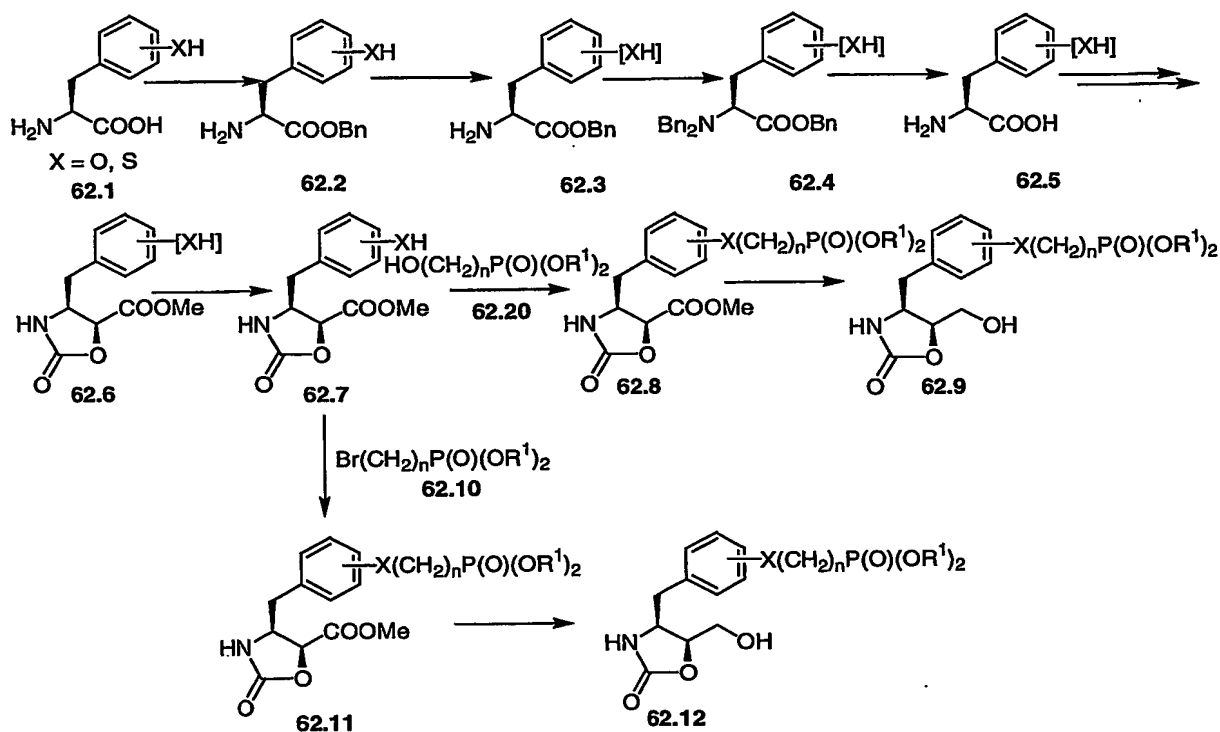


Example

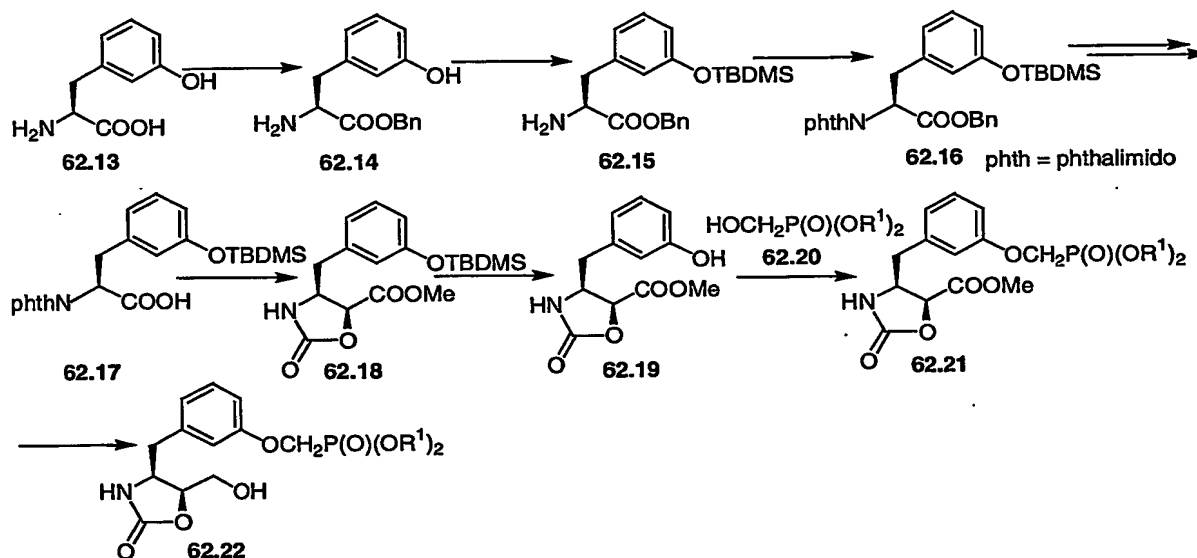


Scheme 62

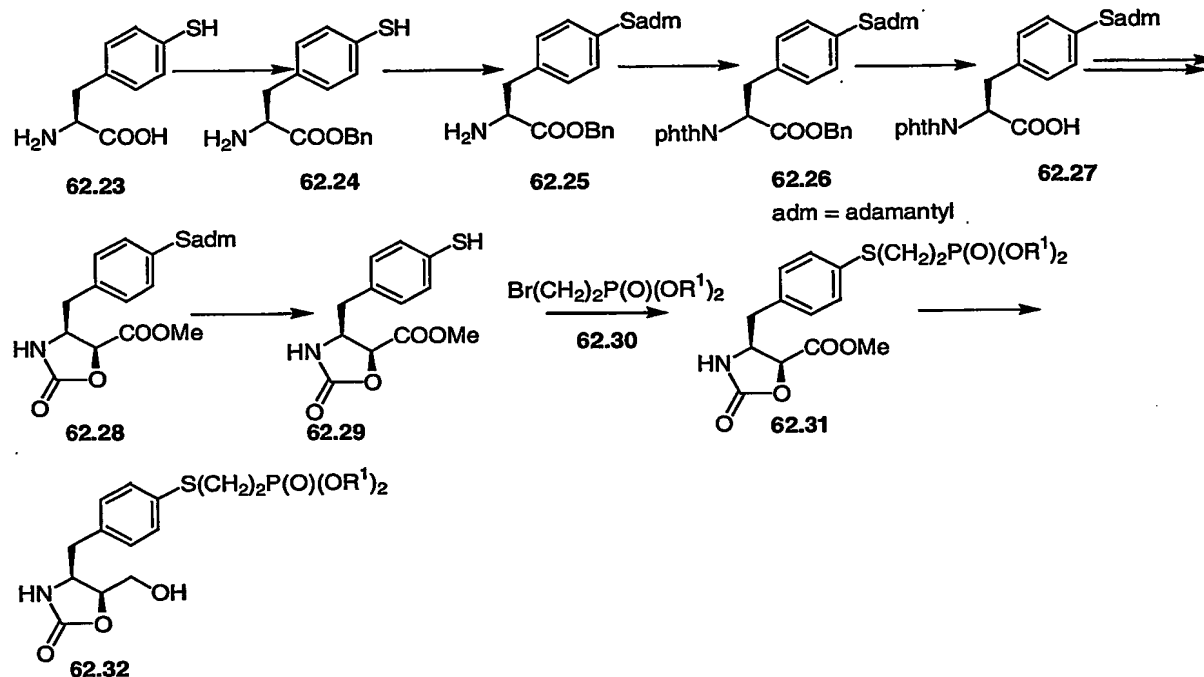
Method



Scheme 62 Example 1



Scheme 62 Example 2



Preparation of the phosphonate-containing thiophenol derivatives 7.2.

- 5 Schemes 63 - 83 describe the preparation of phosphonate-containing thiophenol derivatives 7.2 which are employed as described above (Schemes 7 - 9) in the preparation of the phosphonate ester intermediates 1 in which X is sulfur.

10 Scheme 63 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 63.1 is protected to afford the product 63.2. The protection of phenyl thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a

15 chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in

Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, with a dialkyl phosphite **63.3**, to afford the phosphonate ester **63.4**. The thiol protecting group is then removed, as described above, to afford the thiol **63.5**.

- 5 For example, 3-bromothiophenol **63.6** is converted into the 9-fluorenylmethyl (Fm) derivative **63.7** by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite **63.3**, as described above, to afford the phosphonate ester **63.8**. The Fm protecting group is then removed by treatment of the product with piperidine in
10 dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol **63.9**.

Using the above procedures, but employing, in place of 3-bromothiophenol **63.6**, different thiophenols **63.1**, and/or different dialkyl phosphites **63.3**, the corresponding products **63.5** are obtained.

15

- Scheme **64** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **64.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **64.3**. The latter compound is reacted
20 with a halodialkyl phosphite **64.4** to afford the product **64.5**; deprotection then affords the thiophenol **64.6**

- For example, 4-bromothiophenol **64.7** is converted into the S-triphenylmethyl (trityl) derivative **64.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **64.9**
25 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite **64.10** to afford the phosphonate **64.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **64.12**.

- Using the above procedures, but employing, in place of the bromo compound **64.7**, different
30 halo compounds **64.1**, and/or different halo dialkyl phosphites **64.4**, there are obtained the corresponding thiols **64.6**.

Scheme 65 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 65.1 is subjected to free-radical bromination to afford a bromomethyl product 65.2. This compound is reacted with a sodium dialkyl phosphite 65.3 or a trialkyl phosphite, to give the displacement or rearrangement product 65.4, which upon deprotection affords the thiophenol 65.5.

For example, 2-methylthiophenol 65.6 is protected by conversion to the benzoyl derivative 65.7, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 65.8. This material is reacted with a sodium dialkyl phosphite 65.3, as described in *J. Med. Chem.*, 35, 1371, 1992, to afford the product 65.9. Alternatively, the bromomethyl compound 65.8 is converted into the phosphonate 65.9 by means of the Arbuzov reaction, for example as described in *Handb. Organophosphorus Chem.*, 1992, 115. In this procedure, the bromomethyl compound 65.8 is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate 65.9. Deprotection of the phosphonate 65.9, for example by treatment with aqueous ammonia, as described in *J. Am. Chem. Soc.*, 85, 1337, 1963, then affords the thiol 65.10.

Using the above procedures, but employing, in place of the bromomethyl compound 65.8, different bromomethyl compounds 65.2, there are obtained the corresponding thiols 65.5.

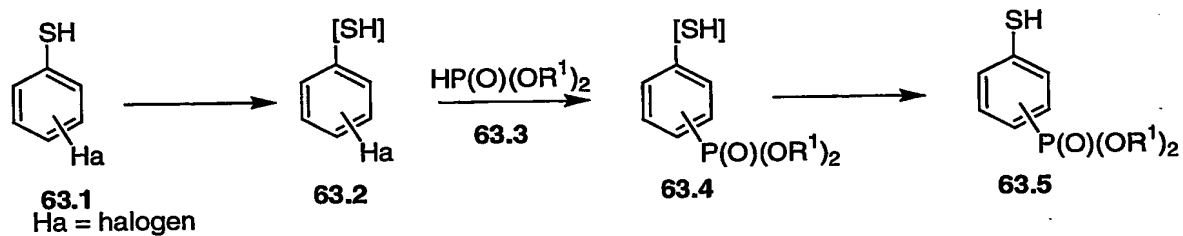
Scheme 66 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 66.1 is reacted with a dialkyl hydroxyalkylphosphonate 66.2 under the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product 66.3. Deprotection then yields the O- or S-linked products 66.4.

For example, the substrate 3-hydroxythiophenol, 66.5, is converted into the monotrityl ether 66.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 66.7 in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound 66.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 66.9.

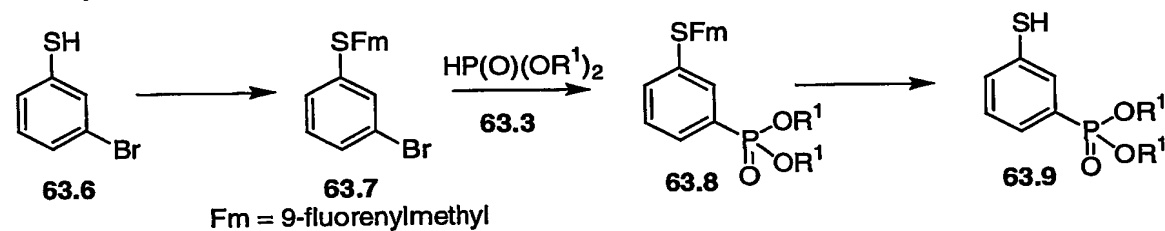
Using the above procedures, but employing, in place of the phenol **66.5**, different phenols or thiophenols **66.1**, there are obtained the corresponding thiols **66.4**.

Scheme 63

Method



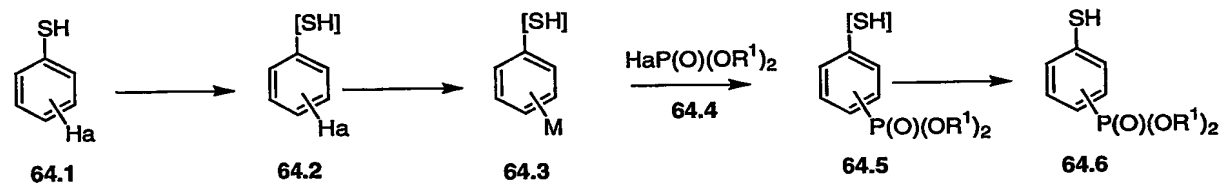
Example



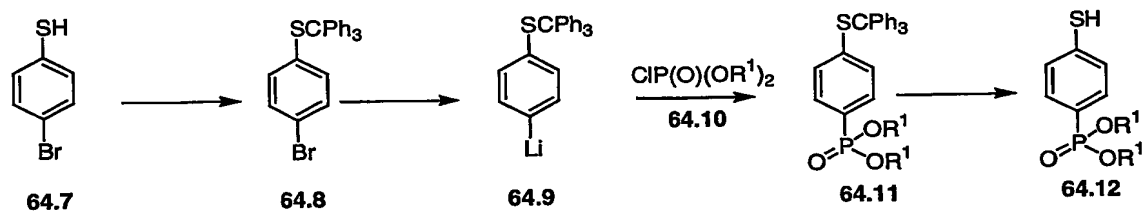
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Scheme 64

Method

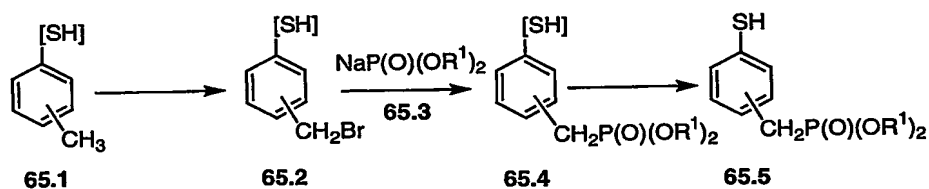


Example

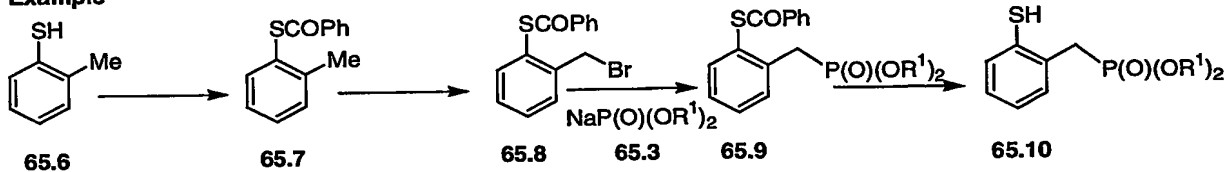


Scheme 65

Method

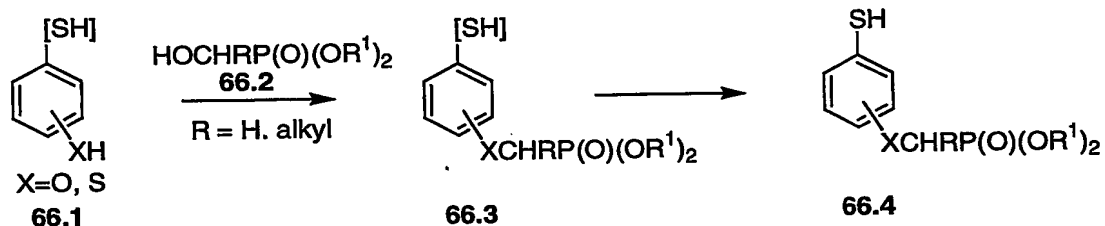


Example

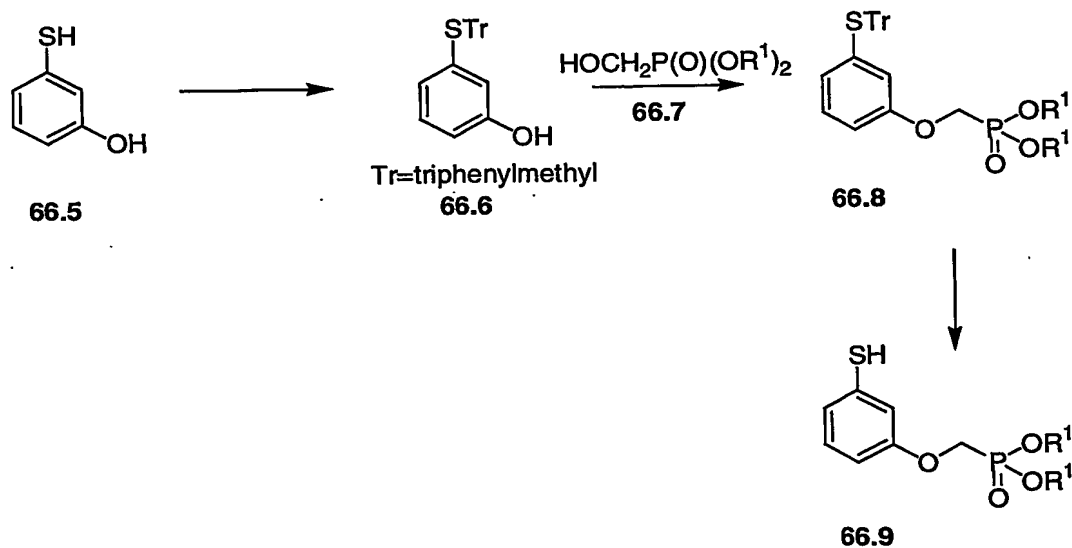


Scheme 66

Method



Example



Scheme 67 illustrates the preparation of thiophenols 67.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 67.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 67.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 67.3. Deprotection then affords the thiol 67.4.

For example, 4-methylaminothiophenol 67.5 is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product 67.6. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate 67.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 67.8. Preferably, equimolar amounts of the phosphonate 67.7 and the amine 67.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 67.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 67.9.

Using the above procedures, but employing, in place of the thioamine 67.5, different phenols, thiophenols or amines 67.1, and/or different phosphonates 67.2, there are obtained the corresponding products 67.4.

Scheme 68 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 68.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 68.1 is reacted with a dialkyl bromoalkyl phosphonate 68.2 to afford the product 68.3. Deprotection then affords the free thiophenol 68.4.

For example, 3-hydroxythiophenol 68.5 is converted into the S-trityl compound 68.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 68.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product **68.8**. Deprotection, as described above, then affords the thiol **68.9**.

Using the above procedures, but employing, in place of the phenol **68.5**, different phenols, thiophenols or amines **68.1**, and/or different phosphonates **68.2**, there are obtained the
5 corresponding products **68.4**.

Scheme **69** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **69.2** is
10 coupled with an aromatic bromo compound **69.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

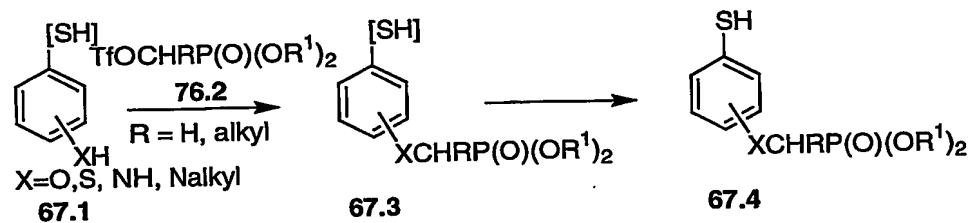
15 tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **69.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **69.4**, or the saturated analog **69.6**.

20 For example, 3-bromothiophenol is converted into the S-Fm derivative **69.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **69.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
25 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **69.9**. Deprotection, as described above, then affords the thiol **69.10**. Optionally, the initially formed unsaturated phosphonate **69.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **69.11**, which upon deprotection affords the thiol **69.12**.

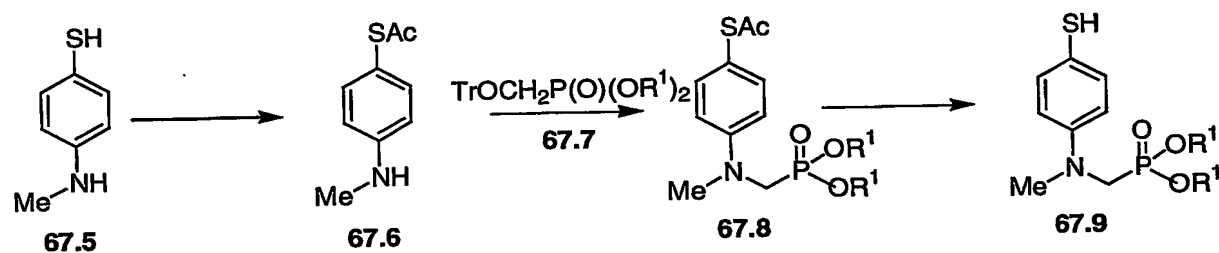
30 Using the above procedures, but employing, in place of the bromo compound **69.7**, different bromo compounds **69.1**, and/or different phosphonates **69.2**, there are obtained the corresponding products **69.4** and **69.6**

Scheme 67

Method

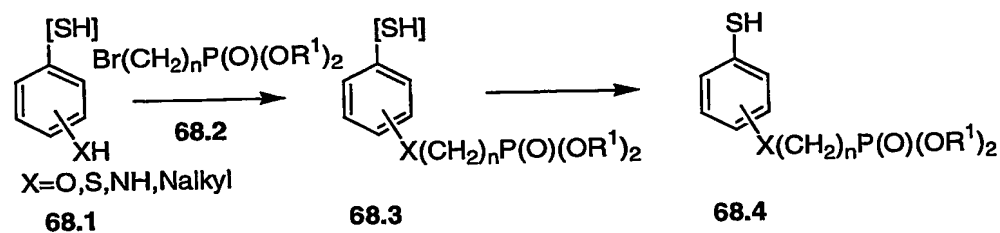


Example

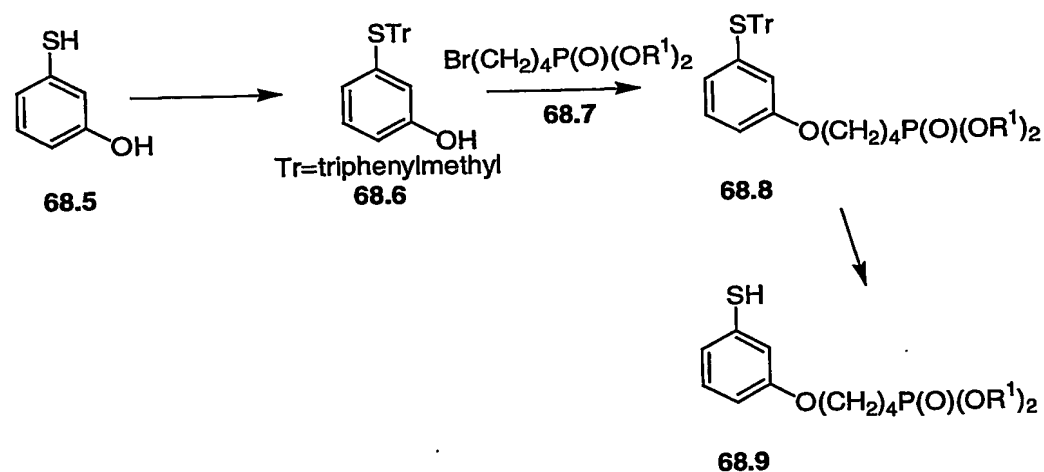


Scheme 68

Method

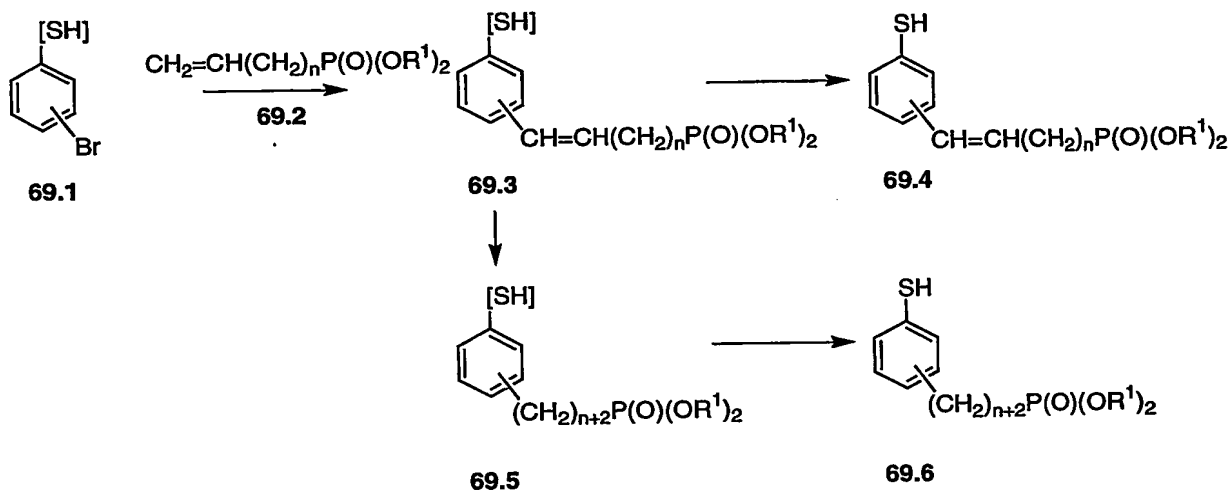


Example

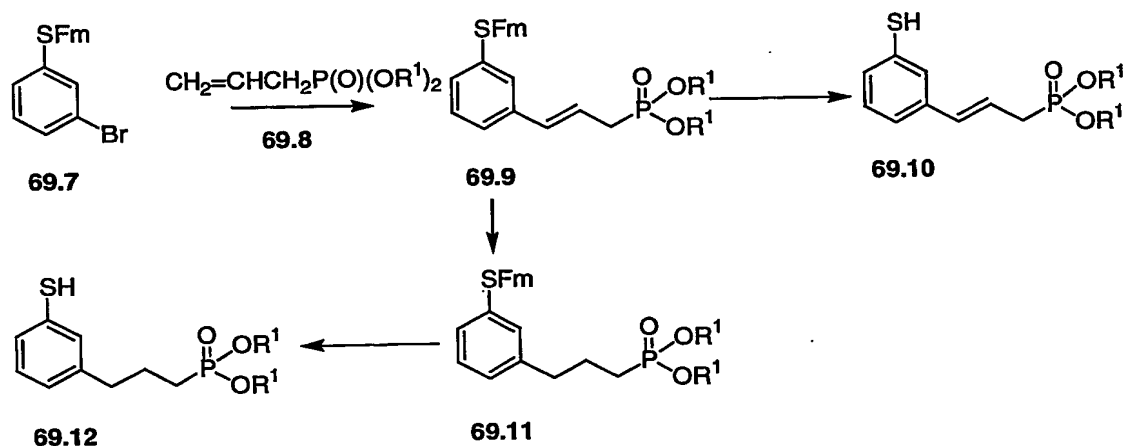


Scheme 69

Method



Example



Scheme 70 illustrates the preparation of an aryl-linked phosphonate ester **70.4** by means of a
 5 palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a
 phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,
 VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **70.1** is obtained by means of a
 metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for
 example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the
 10 diaryl product **70.3** which is deprotected to yield the thiol **70.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,
 in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **70.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **70.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **70.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **70.8**. Using the above procedures, but employing, in place of the boronate **70.5**, different boronates **70.1**, and/or different phosphonates **70.2**, there are obtained the corresponding products **70.4**.

Scheme **71** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **71.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **71.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **71.3** is then deprotected to afford the thiol **71.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **71.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **71.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **71.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **71.7** thus obtained is deprotected, as described above, to afford the thiol **71.8**.

Using the above procedures, but employing, in place of the thiophenol **71.5**, different phenols, thiophenols or amines **71.1**, and/or different phosphonates **71.2**, there are obtained the corresponding products **71.4**.

Scheme **72** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **72.1**, for example an indoline (in which X-Y is (CH₂)₂), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH₂)₃) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **72.2**, in the presence of an

organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **72.3**. Deprotection, as described above, then affords the thiol **72.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding

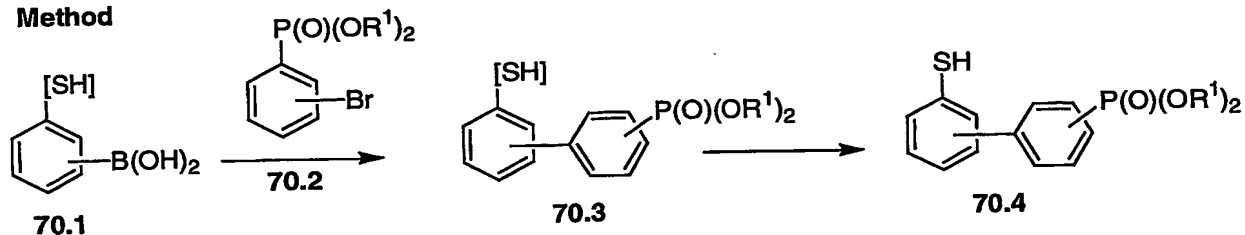
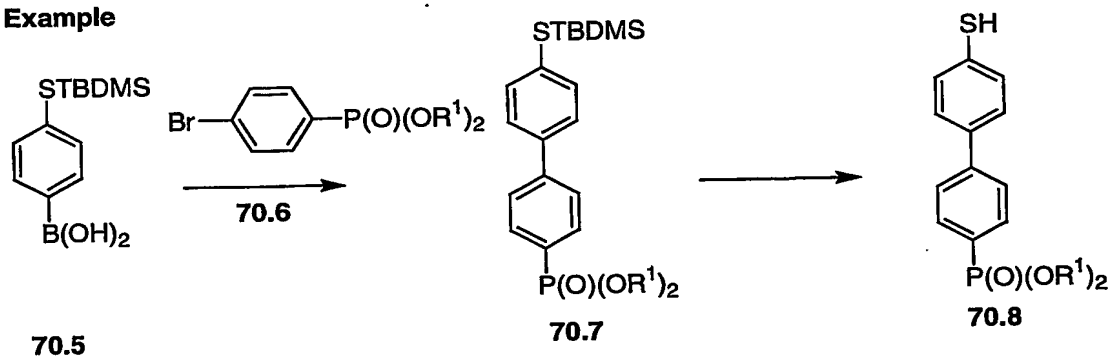
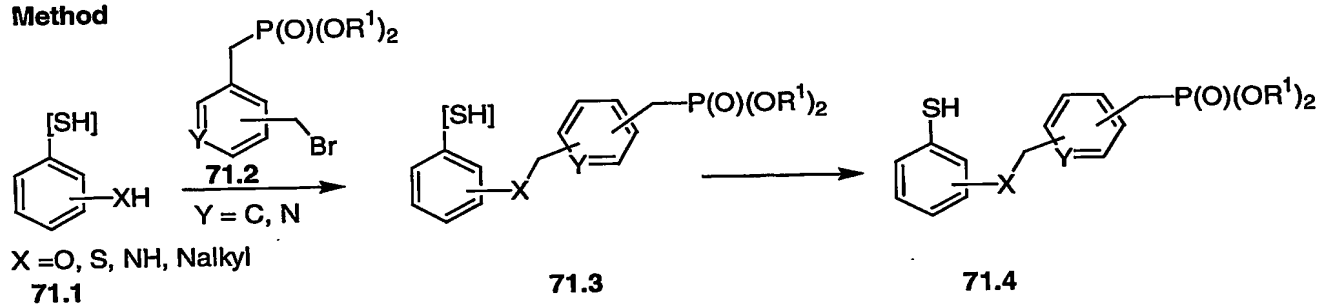
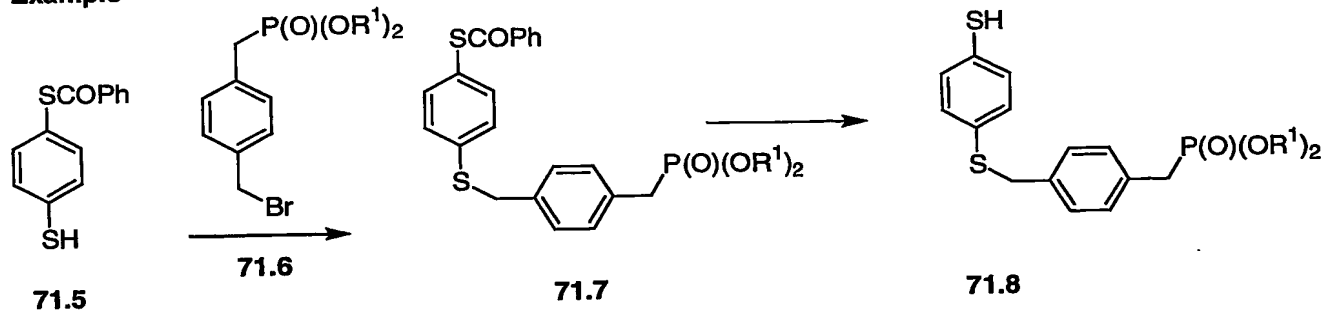
5 hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

10 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

15 For example, 2,3-dihydro-1H-indole-5-thiol, **72.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **72.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **72.7**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, to yield the phosphonate **72.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as

20 described above, then affords the thiol **72.9**.

Using the above procedures, but employing, in place of the thiol **72.5**, different thiols **72.1**, and/or different triflates **72.2**, there are obtained the corresponding products **72.4**.

Scheme 70**Method****Example****Scheme 71****Method****Example**

5 Preparation of phosphonate-containing analogs of isobutylamine 10.2.

Schemes 73 - 75 illustrate the preparation of the phosphonate-containing analogs of isobutylamine which are employed in the preparation of the phosphonate esters 2.

Scheme 73 depicts the preparation of phosphonates which are attached to the isobutylamine by means of an amide linkage. In this procedure, an aminoacid 73.1 is protected to afford the product 73.2. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, 309. Amino groups are protected, for example, by conversion into carbamates such as the tert. butoxycarbamate (BOC) derivative, or by reaction with phthalic anhydride to afford the phthalimido (phth) derivative. The amine-protected aminoacid 73.2 is then coupled with a dialkyl aminoalkyl phosphonate 73.3, to yield the amide 73.4. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolid and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The protecting group is then removed to afford the amine 73.5. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 309ff. For example, BOC groups are removed by treatment with acids such as trifluoroacetic acid, and phthalimido groups are removed by reaction with hydrazine hydrate. For example, 2-methyl-4-aminobutyric acid 73.6 (Acros) is reacted with phthalic anhydride in refluxing toluene, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to give the phthalimido derivative 73.7. The product is coupled with a dialkyl aminoethyl phosphonate 73.8, the preparation of which is described in J. Org. Chem., 2000, 65, 676,

in the presence of dicyclohexyl carbodiimide, to give the amide **73.9**. The protecting group is removed by reaction of the product with ethanolic hydrazine at ambient temperature, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to afford the amine **73.10**.

- 5 Using the above procedures, but employing, in place of the acid **73.6**, different acids **73.1**, and/or different amines **73.3**, the corresponding amides **73.5** are obtained.

10 Scheme **74** depicts the preparation of isobutylamine phosphonates in which the phosphonate is attached by means of an aromatic ring. In this procedure, 2-methyl-but-3-enylamine **74.1**, prepared as described in *Org. Prep. Proc. Int.* 1976, 8, 75, is coupled, in the presence of a palladium catalyst, as described above (Scheme **50**) with a dialkyl bromophenyl phosphonate **74.2** to afford the olefinic product **74.3**. Optionally, the product is reduced to afford the saturated analog **74.4**. The reduction is effected catalytically, for example by the use of a palladium catalyst, or chemically, for example by the use of diimide.

- 15 For example, the amine **74.1** is coupled with a dialkyl 4-bromophenyl phosphonate **74.5**, prepared as described in *J. Organomet. Chem.*, 1999, 581, 62, to yield the product **74.6**. Catalytic hydrogenation in ethanol, using a 5% palladium catalyst, then affords the saturated compound **74.7**.

20 Using the above procedures, but employing, in place of the phosphonate **74.5**, different phosphonates **74.2** the corresponding products **74.3** and **74.4** are obtained.

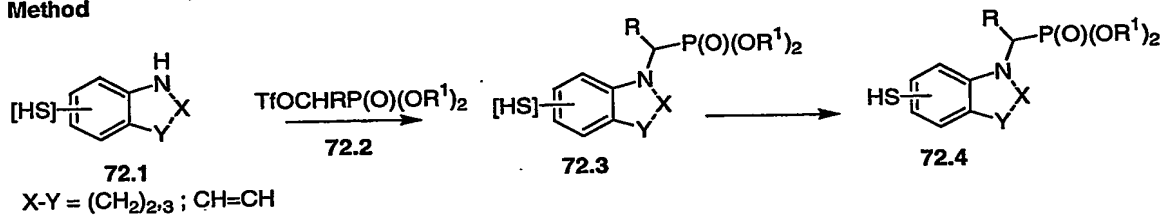
Scheme **75** illustrates the preparation of isobutylamine phosphonates in which the phosphonate group is attached by means of an alkylene chain. In this procedure, a bromoamine **75.1** is protected, as described in Scheme **73**, to afford the derivative **75.2**. The product is then
25 reacted with a trialkyl phosphite **75.3**, in an Arbuzov reaction, as described in Scheme **65**, to give the phosphonate **75.4**. Deprotection then affords the amine **75.5**.

For example, 4-bromo-2-methyl-butylamine **75.6**, prepared as described in *Tet.*, 1998, 54, 2365, is converted, as described above, into the phthalimido derivative **75.7**. The product is then heated at 110° with a trialkyl phosphite **75.3** to yield the phosphonate **75.8**, which upon
30 reaction with ethanolic hydrazine affords the amine **75.9**.

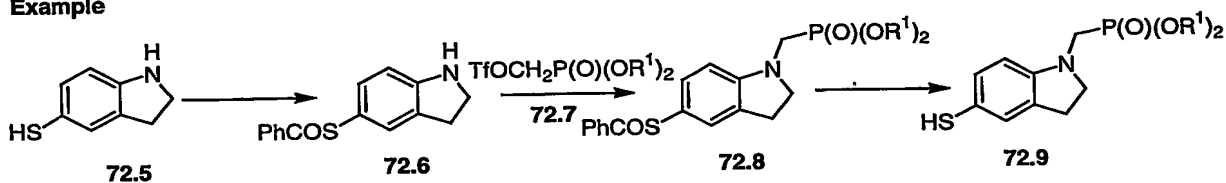
Using the above procedures, but employing, in place of the bromide **75.6**, different bromides **75.1**, and/or different phosphites **75.3**, the corresponding products **75.5** are obtained.

Scheme 72

Method

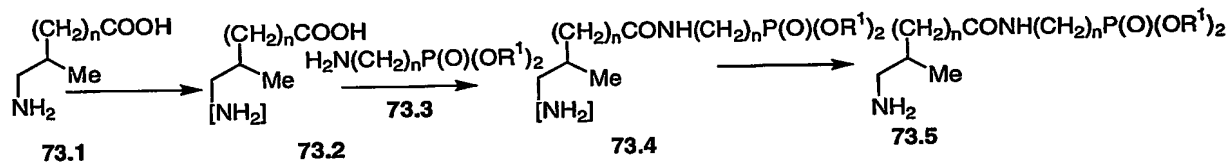


Example

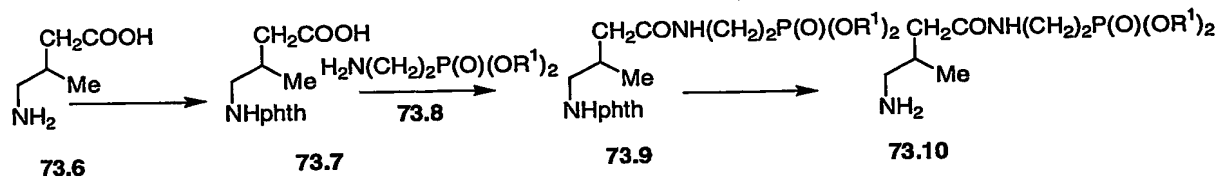


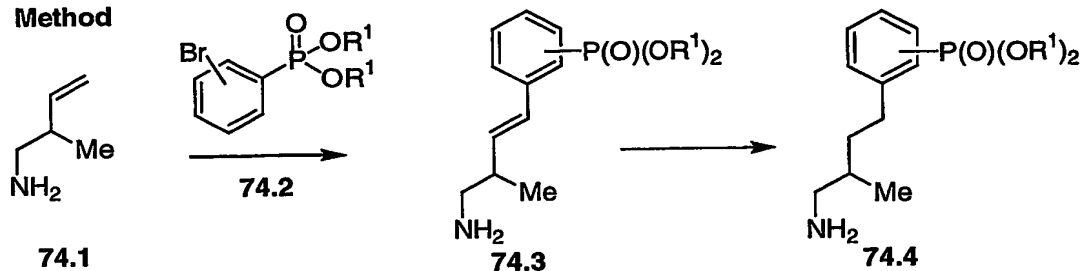
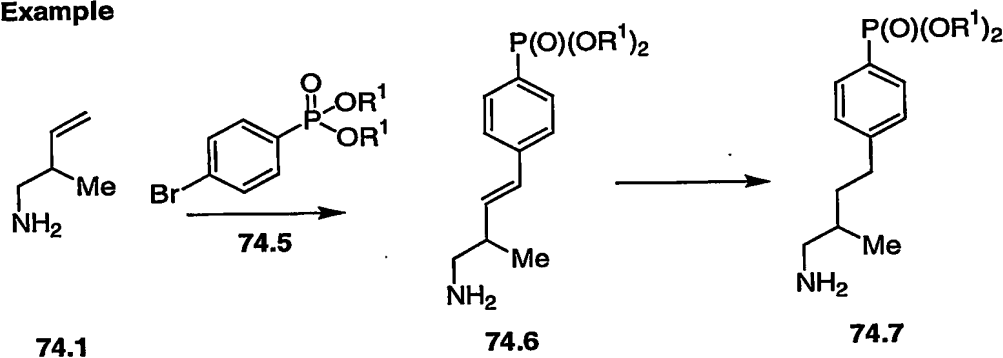
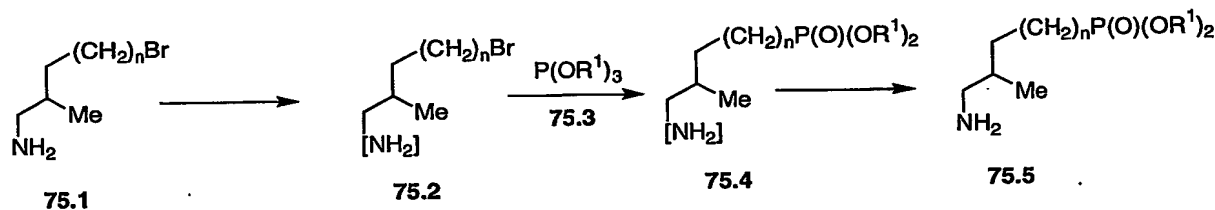
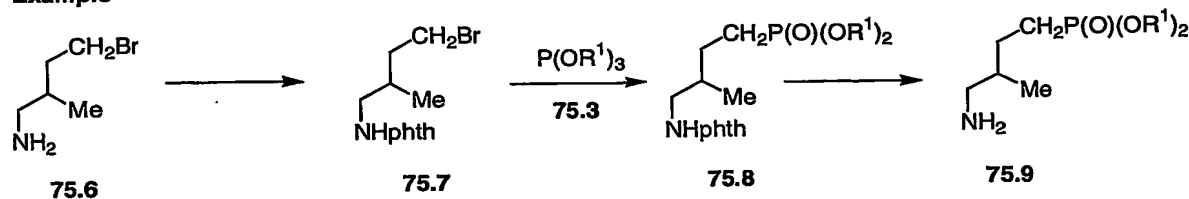
Scheme 73

Method



Example



Scheme 74**Method****Example****Scheme 75****Method****Example****Preparation of cyclopentylmethylamine phosphonates.**

5

Schemes 76 - 78 illustrate the preparation of cyclopentylmethylamine phosphonates which are employed, as shown in Schemes 10 - 12, in the preparation of the phosphonate esters 3.

Scheme 76 depicts the preparation of phosphonates attached to the cyclopentyl ring either directly or by means of an alkoxy link. In this procedure, a hydroxy-substituted

10

cyclopentylmethylamine **76.1** is protected, and the protected derivative **76.2** is converted into the corresponding bromide **76.3**, for example by treatment with carbon tetrabromide and triphenyl phosphine as described in Scheme 59. The bromo compound is then reacted with a trialkyl phosphite **76.4** in an Arbuzov reaction, as described above, to afford the phosphonate **76.5** which is then deprotected to give the amine **76.6**. Alternatively, the protected amine **76.2** is reacted with a dialkyl bromoalkyl phosphonate **76.7** to give the ether **76.8**. The alkylation reaction is conducted at ca 100° in a polar organic solvent such as dimethylformamide in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide. The product is then deprotected to give the amine **76.9**.

For example, 3-aminomethyl-cyclopentanol **76.10**, prepared as described in Tet., 1999, 55, 10815, is converted, as described above, into the phthalimido derivative **76.11**. The product is then converted, as described above, into the bromo analog **76.12**. The latter compound is reacted at ca 120° with a trialkyl phosphite **76.4** to afford the phosphonate **76.13**, which upon deprotection by reaction with hydrazine yields the amine **76.14**.

Using the above procedures, but employing, in place of the bromide **76.12**, different bromides **76.3**, and/or different phosphites **76.4**, the corresponding products **76.6** are obtained.

Alternatively, 2-aminomethyl-cyclopentanol **76.15**, prepared as described in Tet., 1999, 55, 10815, is converted into the phthalimido derivative **76.16**. The product is then reacted in dimethylformamide solution with an equimolar amount of a dialkyl bromopropyl phosphonate **76.17**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and sodium hydride, to give the ether **76.18**. Deprotection, as described above, then affords the amine **76.19**.

Using the above procedures, but employing, in place of the carbinol **76.15**, different carbinols **76.1**, and/or different phosphonates **76.7**, the corresponding products **76.9** are obtained.

Scheme 77 illustrates the preparation of cyclopentylmethylamines in which the phosphonate group is attached by means of an amide group. In this procedure, a carboxyalkyl-substituted cyclopentylmethylamine **77.1** is protected to afford the derivative **77.2**. The product is then coupled, as described above, (Scheme 1) with a dialkyl aminoalkyl phosphonate **77.3** to yield the amide **77.4**. Deprotection then affords the amine **77.5**.

For example, 3-aminomethyl-cyclopentanecarboxylic acid **77.6** prepared as described in J. Chem. Soc. Perkin 2, 1995, 1381, is converted into the BOC derivative **77.7**, by reaction with BOC anhydride in aqueous sodium hydroxide, as described in Proc. Nat. Acad. Sci., 69, 730,

1972. The product is then coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate **77.8** to produce the amide **77.9**. Removal of the BOC group, for example by treatment with hydrogen chloride in ethyl acetate, then affords the amine **77.10**. Using the above procedures, but employing, in place of the carboxylic acid **77.6**, different carboxylic acids **77.1**, and/or different phosphonates **77.3**, the corresponding products **77.5** are obtained.

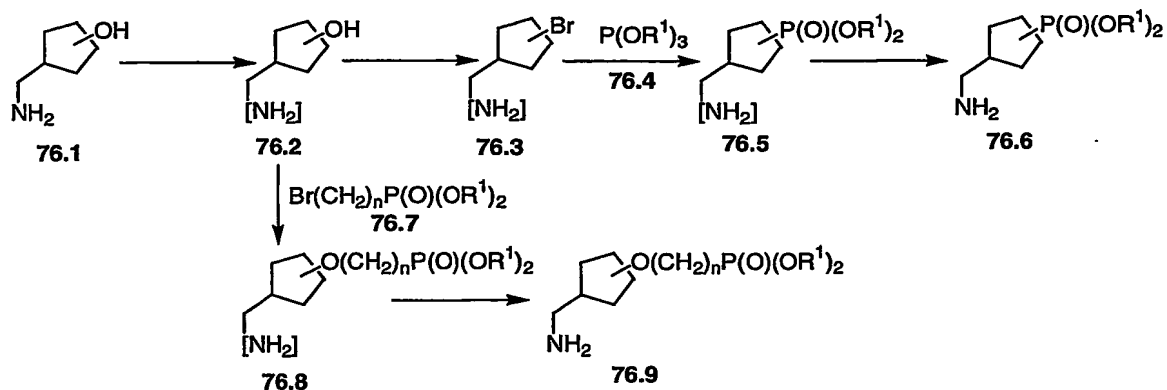
Scheme **78** illustrates the preparation of cyclopentylmethyamines in which the phosphonate group is attached by means of an aminoalkyl group. In this procedure, the more reactive amino group of an amino-substituted cyclopentylmethyamine **78.1** is protected, to give the derivative **78.2**. The product is then coupled, by means of a reductive amination reaction, as described in Scheme **55**, with a dialkyl formylalkyl phosphonate **78.3** to give the amine product **78.4**, which upon deprotection affords the amine **78.5**.

For example, 2-aminomethyl-cyclopentylamine **78.6** prepared as described in WO 9811052, is reacted with one molar equivalent of phthalic anhydride in refluxing tetrahydrofuran, to yield the phthalimido derivative **78.7**. The latter compound is reacted, in the presence of sodium cyanoborohydride, with a dialkyl formylmethyl phosphonate **78.8**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, to afford the product **78.9**. Deprotection, as described above, then yields the amine **78.10**.

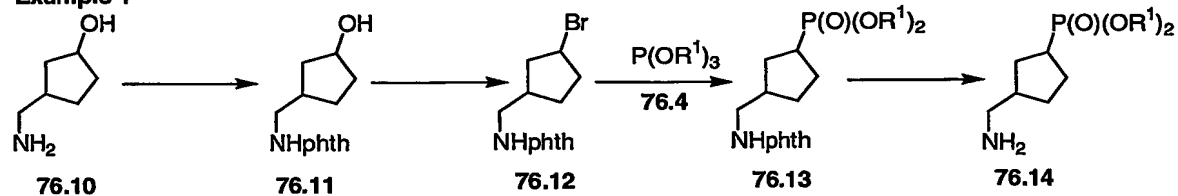
Using the above procedures, but employing, in place of the diamine **78.6**, different diamines **78.1**, and/or different phosphonates **78.3**, the corresponding products **78.5** are obtained.

Scheme 76

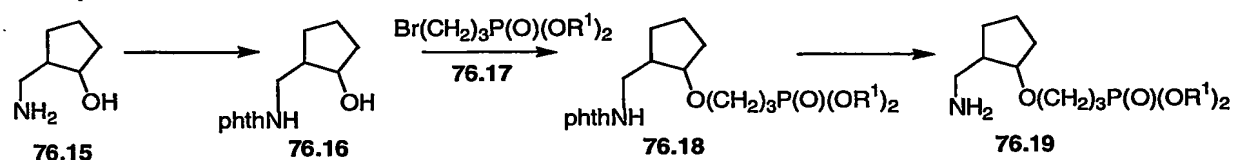
Method



Example 1

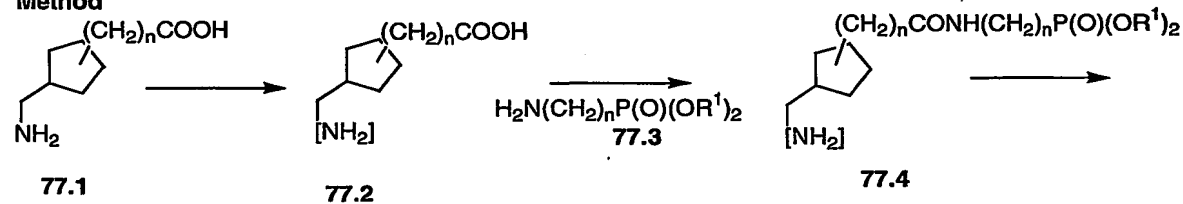


Example 2

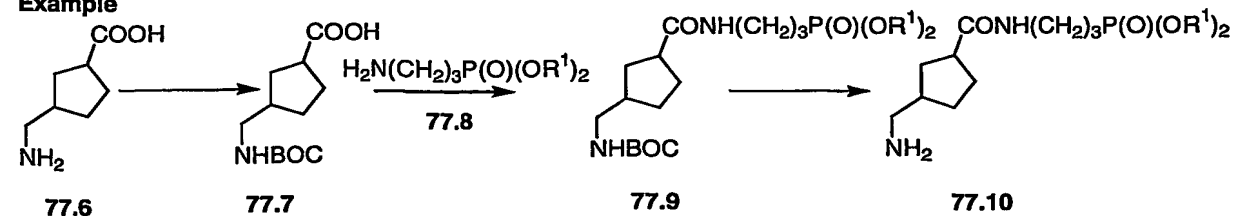


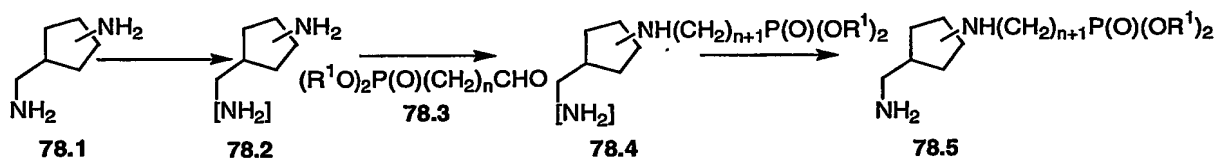
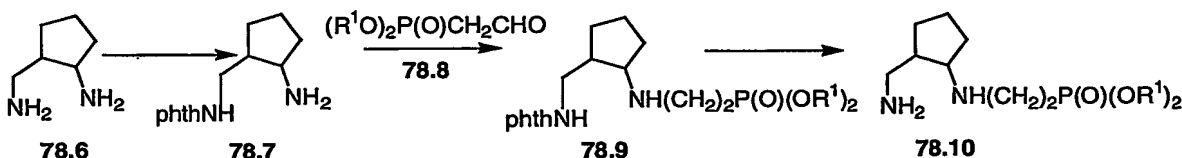
Scheme 77

Method



Example



Scheme 78**Method****Example****Preparation of phosphonate-substituted fluorobenzylamines 39.2.**

5

Schemes 79 and 80 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines **39.2** which are used in the preparation of the phosphonate esters **6**.

Scheme 79 depicts the preparation of fluorobenzylamines in which the phosphonate is attached by means of an amide or aminoalkyl linkage. In this procedure, the more reactive amino group in an amino-substituted 3-fluorobenzylamine **79.1** is protected. The product **79.2** is then coupled with a dialkyl carboxyalkyl phosphonate **79.3** to give the amide **79.4**, which upon deprotection yields the free amine **79.5**. Alternatively, the mono-protected diamine **79.2** is coupled, under reductive amination conditions, with a dialkyl formylalkyl phosphonate **79.6**, to produce the amine **79.7**, which upon deprotection affords the benzylamine **79.8**.

15

For example, 4-amino-3-fluorobenzylamine **79.9**, prepared as described in WO 9417035, is reacted in pyridine solution with one molar equivalent of acetic anhydride, to give the acetilamino product **79.10**. The product is reacted with a dialkyl carboxyethyl phosphonate **79.11**, (Epsilon) and dicyclohexyl carbodiimide, to afford the amide **79.12**. Deprotection, for example by reaction with 85% hydrazine, as described in J. Org. Chem., 43, 4593, 1978, then gives the amine **79.13**.

20

Using the above procedures, but employing, in place of the diamine **79.9**, different diamines **79.1**, and/or different phosphonates **79.3**, the corresponding products **79.5** are obtained.

25

As a further example, the mono-protected diamine **79.10** is reacted, as described above, with a dialkyl formyl phosphonate **79.13**, (Aurora) and sodium cyanoborohydride, to give the amination product **79.14**. Deprotection then affords the amine **79.15**.

Using the above procedures, but employing, in place of the diamine **79.10** different diamines **79.2**, and/or different phosphonates **79.6**, the corresponding products **79.8** are obtained.

Scheme **80** depicts the preparation of fluorobenzylamines in which the phosphonate is attached either directly or by means of a saturated or unsaturated alkylene linkage. In this procedure, a bromo-substituted 3-fluorobenzylamine **80.1** is protected. The product **80.2** is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme **50**, with a dialkyl alkenyl phosphonate **80.3**, to give the olefinic product **80.4** which upon deprotection affords the amine **80.5**. Optionally, the double bond is reduced, for example by catalytic

hydrogenation over a palladium catalyst, to yield the saturated analog **80.9**. Alternatively, the protected bromobenzylamine **80.6** is coupled, as described in Scheme **61**, in the presence of a palladium catalyst, with a dialkyl phosphite **80.6** to produce the phosphonate **80.7**.

Deprotection then affords the amine **80.8**.

For example, 2-bromo-5-fluorobenzylamine **80.10**, (Esprix Fine Chemicals) is converted, as described above, into the N-acetyl derivative **80.11**. The product is the coupled in dimethylformamide solution with a dialkyl vinyl phosphonate **80.12**, (Fluka) in the presence of palladium (II) acetate and triethylamine, to give the coupled product **80.13**. Deprotection then affords the amine **80.14** and hydrogenation of the latter compound yields the saturated analog **80.15**.

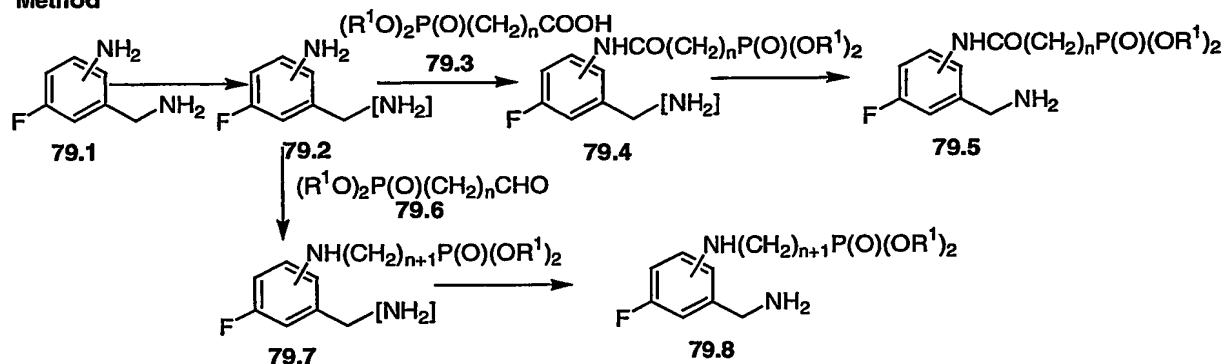
Using the above procedures, but employing, in place of the bromo compound **80.10** different bromo compounds **80.1**, and/or different phosphonates **80.3**, the corresponding products **80.5** and **80.9** are obtained.

As a further example, the protected amine **80.11** is coupled, in toluene at 100°, with a dialkyl phosphite **80.6**, in the presence of tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine, to give the phosphonate **80.16**. Deprotection then affords the amine **80.17**.

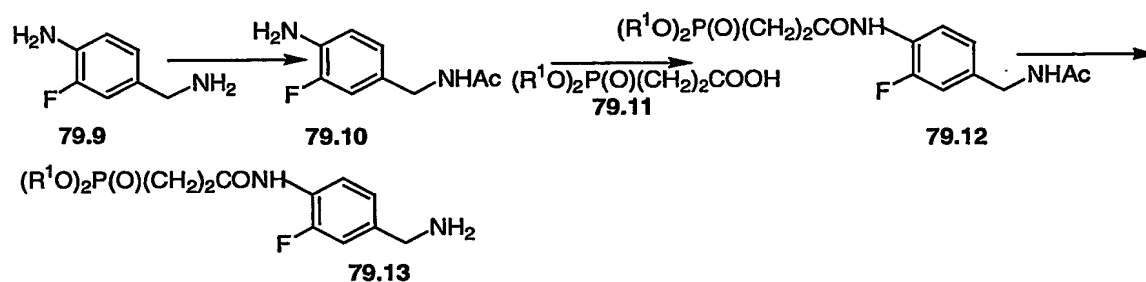
Using the above procedures, but employing, in place of the bromo compound **80.11** different bromo compounds **80.2**, and/or different phosphites **80.6**, the corresponding products **80.8** are obtained.

Scheme 79

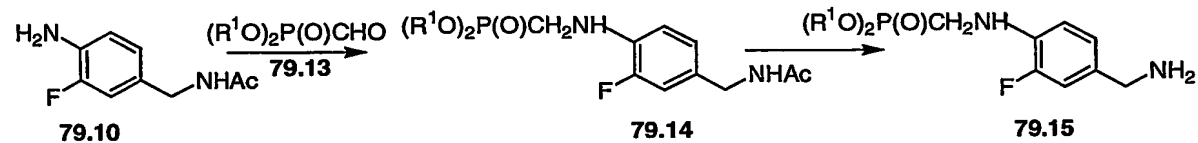
Method



Example 1

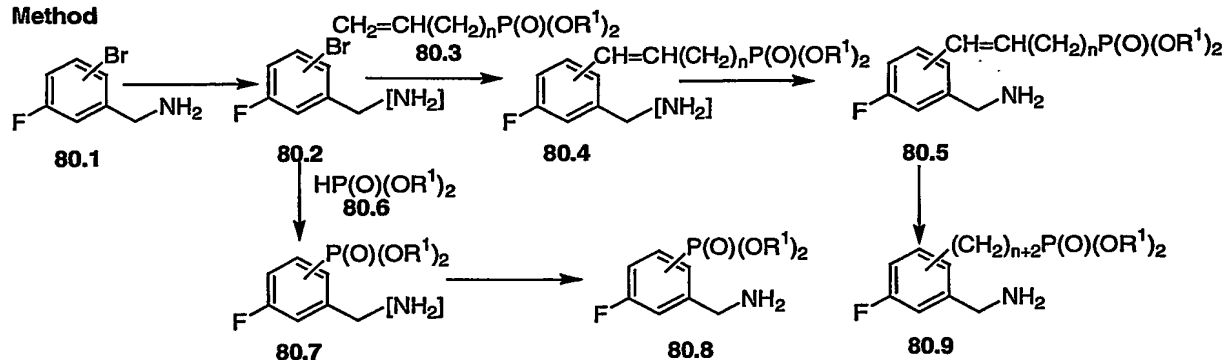


Example 2

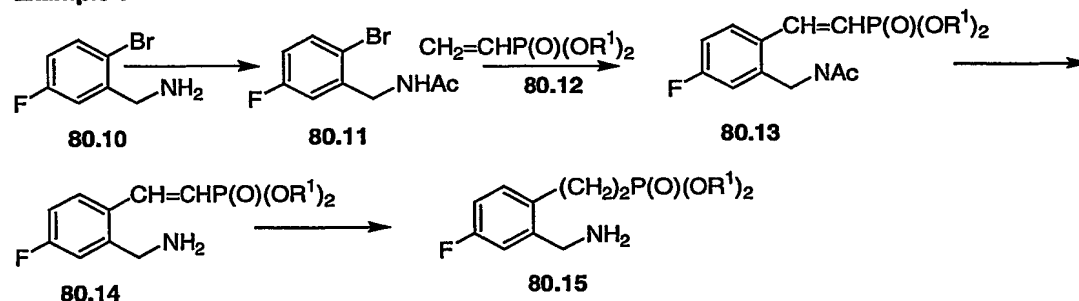


Scheme 80

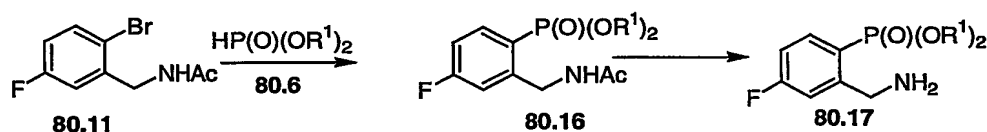
Method



Example 1



Example 2



Preparation of phosphonate-substituted fluorobenzylamines 39.4.

- 5 Schemes 81 and 82 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines 39.4 which are used in the preparation of the phosphonate esters 7.

Scheme 81 depicts the preparation of 3-fluorobenzylamines in which the phosphonate group is attached by means of an amide linkage. In this procedure, 3-fluorophenylalanine 81.1, (Alfa Aesar) is converted into the BOC derivative 81.2. The product is then coupled with a dialkyl aminoalkyl phosphonate 81.3 to afford the amide 81.4, which upon deprotection gives the amine 81.5.

For example, the BOC-protected aminoacid 81.2 is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminomethyl phosphonate 81.6 (Interchim), to prepare the amide 81.7. Deprotection then affords the amine 81.8.

Using the above procedures, but employing, in place of the amine **81.6** different amines **81.3**, the corresponding products **81.5** are obtained.

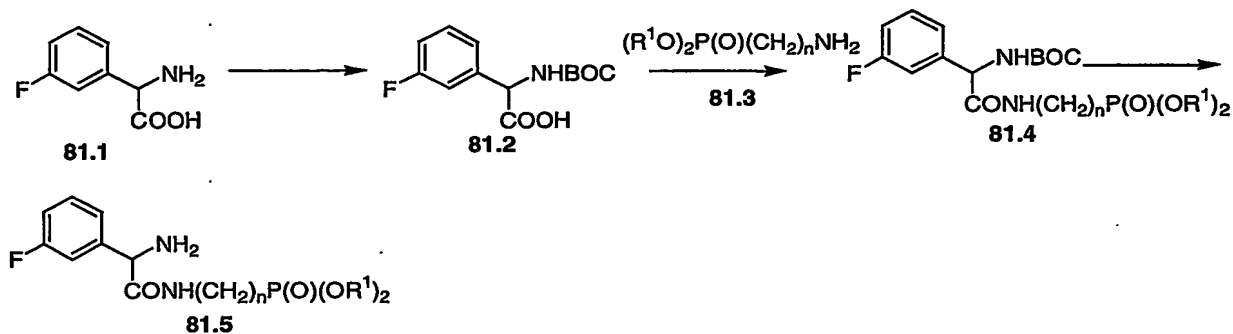
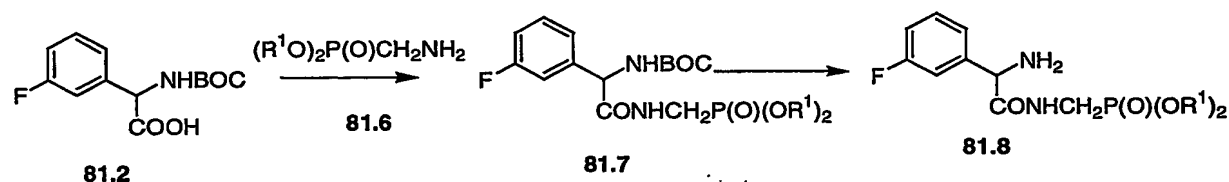
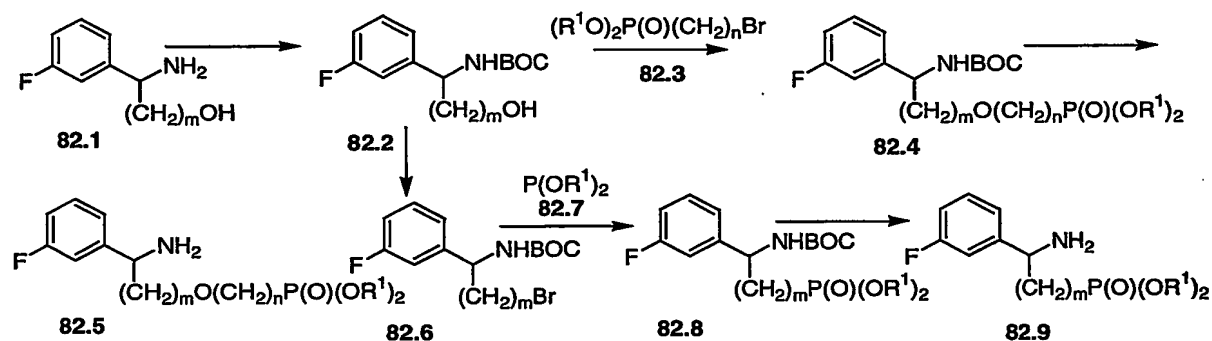
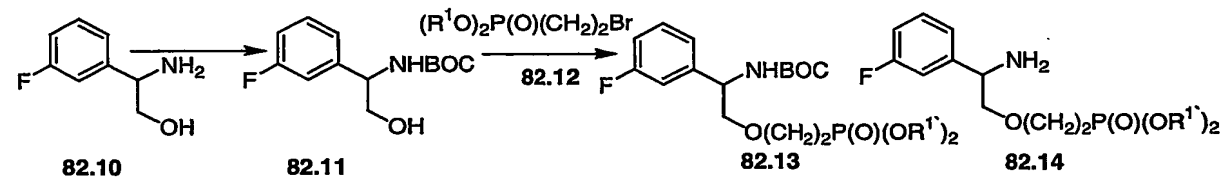
Scheme **82** illustrates the preparation of fluorobenzylamine derivatives in which the phosphonate group is attached by means of an alkyl or alkoxy chain. In this procedure, a hydroxyalkyl-substituted 3-fluorobenzylamine **82.1** is converted into the BOC derivative **82.2**. This compound is then reacted with a dialkyl bromoalkyl phosphonate **82.3** to give the ether **82.4**. The alkylation reaction is conducted in a polar organic solvent such as N-methylpyrrolidinone in the presence of a strong base such as sodium bis(trimethylsilyl)amide.

Deprotection of the product then affords the amine **82.5**. Alternatively, the N-protected carbinol **82.2** is converted into the corresponding bromide **82.6**, for example by reaction with N-bromoacetamide and triphenyl phosphine. The bromo compound is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described above, to give the phosphonate **82.8**, which upon deprotection affords the amine **82.9**.

For example, 2-amino-2-(3-fluoro-phenyl)-ethanol **82.10**, prepared as described in DE 4443892, is converted into the BOC derivative **82.11**. The latter compound is then reacted in dimethylformamide at 100° with a dialkyl bromoethyl phosphonate **82.12** (Aldrich) and sodium hydride, to give the ether product **82.13**. Removal of the BOC group then yields the amine **82.14**.

Using the above procedures, but employing, in place of the carbinol **82.10** different carbinols **82.1**, and/or different phosphonates **82.3** the corresponding products **82.5** are obtained. As a further example, the BOC-protected carbinol **82.11** is reacted with carbon tetrabromide and triphenylphosphine to produce the bromo compound **82.15**. This material is heated at 120° with an excess of a trialkyl phosphite **82.7** to give the phosphonate **82.16**. Deprotection then yields the amine **82.17**.

Using the above procedures, but employing, in place of the carbinol **82.11** different carbinols **82.2**, and/or different phosphonates **82.7** the corresponding products **82.9** are obtained.

Scheme 81**Method****Example****Scheme 82****Method****Example 1****5 Preparation of the phosphonate-containing tert. butanol derivatives 30.1.**

Schemes 83 - 86 illustrate the preparation of the tert. butanol derivatives **30.1** which are employed in the preparation of the phosphonate esters **5**.

Scheme 83 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an alkylene chain. In this procedure, a bromoalkyl carbinol 83.1 is reacted with a trialkyl phosphite 83.2 in an Arbuzov reaction, to afford the phosphonate 83.3.

5 For example, 4-bromo-2-methyl-butan-2-ol 83.4 prepared as described in Bioorg. Med. Chem. Lett., 2001, 9, 525, and a trialkyl phosphite 83.2 are heated at ca. 120° to produce the phosphonate 83.5.

Using the above procedures, but employing, in place of the bromo compound 83.4 different bromo compounds 83.1, and/or different phosphites 83.2 the corresponding products 83.3 are
10 obtained.

Scheme 84 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an amide linkage. In this procedure, a carboxylic acid 84.1 is coupled with a dialkyl aminoalkyl phosphonate 84.2 to afford the amide 84.3. The reaction is
15 conducted under the conditions previously described (Scheme 1) for the preparation of amides.

For example, equimolar amounts of 3-hydroxy-3-methyl-butyric acid 84.4, (Fluka) and a dialkyl aminoethyl phosphonate 84.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted in tetrahydrofuran in the presence of dicyclohexylcarbodiimide to
20 yield the amide 84.6.

Using the above procedures, but employing, in place of the carboxylic acid 84.4 different acids 84.1, and/or different amines 84.2 the corresponding products 84.3 are obtained.

Scheme 85 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted carbinol 85.1 is reacted with a dialkyl bromoalkyl phosphonate 85.2 to afford the ether, thioether or amine products 85.3. The reaction is conducted in a polar organic solvent in the presence of suitable base such as sodium hydride or cesium carbonate. For example, 4-mercapto-2-methyl-butan-2-ol 85.4 prepared as described in Bioorg. Med.
25 Chem. Lett., 1999, 9, 1715, is reacted in tetrahydrofuran containing cesium carbonate with a dialkyl bromobutyl phosphonate 85.5, the preparation of which is described in Synthesis, 1994, 9, 909, to yield the thioether 85.6.
30

Using the above procedures, but employing, in place of the thiol **85.4** different alcohols, thiol or amines **85.1**, and/or different bromides **85.2** the corresponding products **85.3** are obtained.

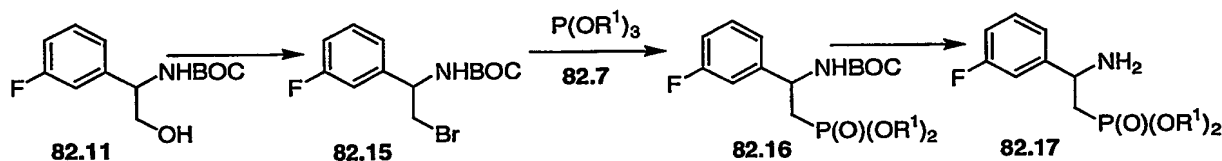
Scheme **86** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a nitrogen and an alkylene chain. In this procedure, a hydroxyaldehyde **86.1** is reacted with a dialkyl aminoalkyl phosphonate **86.2** under reductive amination conditions, as described above, (Scheme **55**) to afford the amine **86.3**.

For example, 3-hydroxy-3-methyl-butyraldehyde **86.4** and a dialkyl aminoethyl phosphonate **86.5** the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted together in the presence of sodium triacetoxyborohydride, to yield the amine **86.6**.

Using the above procedures, but employing, in place of the aldehyde **86.4** different aldehydes **86.1**, and/or different amines **86.2** the corresponding products **86.3** are obtained.

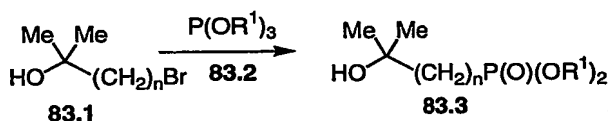
Scheme 82

Example 2

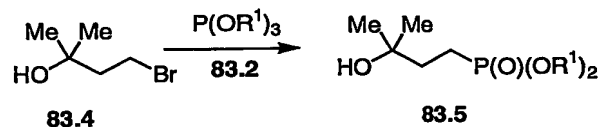


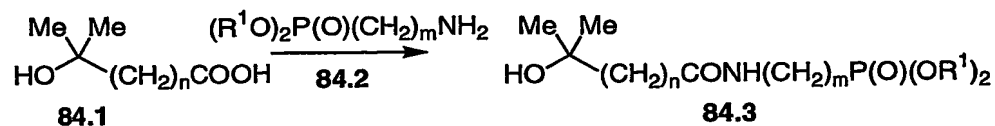
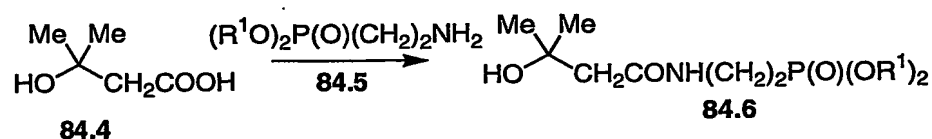
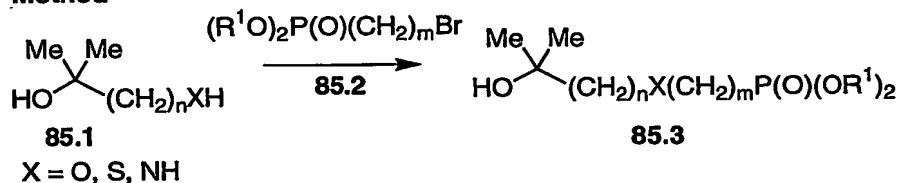
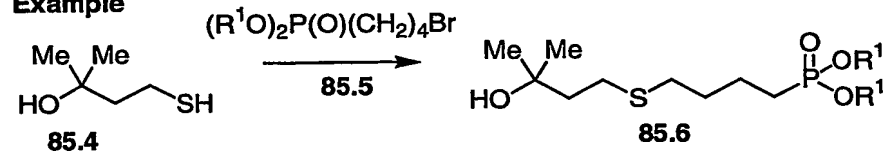
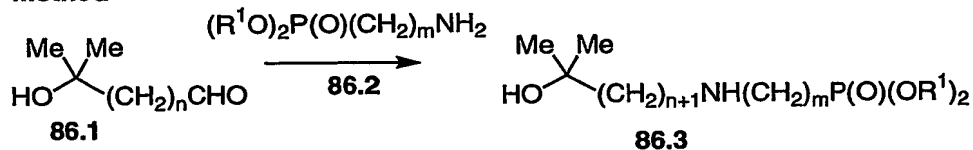
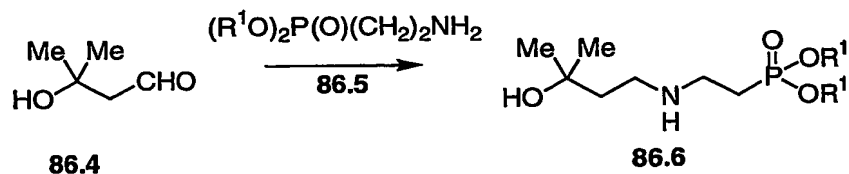
Scheme 83

Method



Example



Scheme 84**Method****Example****Scheme 85****Method****Example****Scheme 86****Method****Example****5 Preparation of the phosphonate-containing benzyl carbamates 43.4.**

Schemes 87 - 91 illustrate methods for the preparation of the benzyl carbamates 43.4 which are employed in the preparation of the phosphonate esters 9. The benzyl alcohols are obtained

by reduction of the corresponding benzaldehydes, the preparation of which is described in Schemes 87 - 90.

Scheme 87 illustrates the preparation of benzaldehyde phosphonates 87.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 87.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 87.2, under reductive amination conditions, as described above in Scheme 55, to yield the phosphonate product 87.3.

For example, benzene-1,3-dialdehyde 87.4 is reacted with a dialkyl aminopropyl phosphonate 87.5, (Acros) and sodium triacetoxyborohydride, to afford the product 87.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 87.4, different benzene dialdehydes 87.1, and/or different phosphonates 87.2, the corresponding products 87.3 are obtained.

Scheme 88 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde 88.1 is coupled, as described above, with a dialkyl alkenylphosphonate 88.2, to afford the alkenyl phosphonate 88.3. Optionally, the product is reduced to afford the saturated phosphonate ester 88.4. Alternatively, the bromobenzaldehyde is coupled, as described above, with a dialkyl phosphite 88.5 to afford the formylphenylphosphonate 88.6.

For example, as shown in Example 1, 3-bromobenzaldehyde 88.7 is coupled with a dialkyl propenylphosphonate 88.8 (Aldrich) to afford the propenyl product 88.9. Optionally, the product is reduced, for example by the use of diimide, to yield the propyl phosphonate 88.10.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde 88.7, different bromobenzaldehydes 88.1, and/or different alkenyl phosphonates 88.2, the corresponding products 88.3 and 88.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 88.5 to afford the 4-formylphenyl phosphonate product 88.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 88.11, different bromobenzaldehydes 88.1, the corresponding products 88.6 are obtained.